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The Invention, Dissemination, and Application of
Organ Replacement Therapy in late-Victorian Medical
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DURHAM UNIVERSITY

AT THE INTERSECTION OF THE CLINIC AND THE LABORATORY

The Invention, Dissemination, and
Application of Organ Replacement Therapy
in late-Victorian Medical Culture

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Submitted for the degree of PhD in Philosophy

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THESIS ABSTRACT

This thesis re-evaluates the initial use of organ replacement therapy in Britain during the 1890s with regard to the thyroid gland and the associated disease entity of myxoedema as paradigmatic examples. The scope of my argument, however, encompasses the period between the 1850s and 1910s, as it approaches this subject from three perspectives. Firstly, this thesis examines the difficult and multifaceted history of thyroid insufficiency disorders between 1850 and 1878, such as endemic cretinism and goitre. Secondly, the introduction of myxoedema as a distinct clinical entity between 1878 and 1888 is discussed. Finally, the professional debates surrounding the new therapeutic approach of organ replacement therapy and its clinical application and scientific assessment are analysed for the period from the 1890s onward.

By focussing on the notions of disease causation via key historical figures and their publications, I argue that there was a mutual influence between the conception of myxoedema and organ replacement therapy, and that neither one would otherwise have become acceptable by the standards of late-nineteenth and early-twentieth-century scientific medicine. The origins of the ensemble of the new concepts and practices that constitute myxoedema and the associated organ replacement therapy can thereby be situated within a specific timeframe and context. They did not simply arise from contemporary medical knowledge, nor were they the culmination of some long-held desire of the medical community, or solely the result of medical progress. Instead, the practice of organ replacement therapy, as well as the new disease entity of myxoedema, depended on a view of the human body that assumed the medical possibility and desirability of replacing an organ's lost function.

This view was part of the concept of organ replacement, which emerged in the specific context of an experiment-oriented style of university medicine that predominated in the late nineteenth and early twentieth centuries. Its emergence depended on contemporary clinical and scientific practices as well as on the institutional and epistemological context within which these practices were embedded. As this thesis demonstrates, various social, scientific, and technical conditions needed to concur before organ replacement therapy could become part of medical reality.

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TABLE OF CONTENTS

Abstract	i
Acknowledgements.....	ii
Introduction.....	1
Contextualising Organ Replacement Therapy and Thyroid Studies.....	3
The De-Historisation of Organ Replacement Therapy	10
Points of Departure for a Historical Consideration.....	16
Rationale and Thesis Structure	21
 Chapter 1 Redefining Cretinism and Goitre: The Beginning of the Thyroid Insufficiency Concept	 29
1.1. Introduction.....	29
1.2. Cretinism.....	31
1.3. The Methodological Problem of Causal Attribution	36
1.4. Goitre and the Invention of the Surgical Thyroid Replacement Therapy	44
1.5. “Old” and “New” Cretinism: From Endemic to Sporadic Cretinism	55
1.6. The Problem of Causal Attribution: Sporadic Cretinism and the Thyroid Gland.....	64
1.7. Conclusion	67
 Chapter 2 Clinical Observation: William Ord and the Origins of Myxoedema	 69
2.1. Introduction.....	69
2.2. Introducing Myxoedema	70
2.3. Negotiating Myxoedema: Establishing the Committee of the Clinical Society.....	80
2.4. Establishing the Clinical Picture of Myxoedema	85
2.5. Conclusion	91
 Chapter 3 Scientific Analysis: Victor Horsley and Thyroid Replacement.....	 93
3.1. Introduction.....	93
3.2. Developing a Pathological Concept of the Thyroid.....	95
3.3. Correlating Myxoedema, Cachexia Strumipriva, and Sporadic Cretinism: Victor Horsley’s Animal Experiments and Diagnostic Field Work.....	100
3.4. The (Im-)Possible Path to Therapy.....	107
3.5. Conclusions of the Final Report of the Myxoedema Committee.....	114
3.6. Conclusion	117

Chapter 4	Experimentation: Organotherapy and the Treatment of Myxoedema	120
4.1.	Introduction	120
4.2.	The Concept of Organotherapy	122
4.3.	British Physicians and 'Internal Secretion'	127
4.4.	The Therapeutic Turning Point	133
4.5.	Thyroid Extract and the Treatment of Myxoedema	138
4.6.	A 'Rational' Therapy	143
4.7.	Organ Replacement Therapy as a Method in Britain	146
4.8.	Organ Replacement Therapy and Thyroid Juice	148
4.9.	Conclusion	153
Chapter 5	At the Interface of Clinic and University: The Medical Profession and Organ Replacement Therapy	155
5.1.	Introduction	155
5.2.	Changing Styles in Medicine	156
5.3.	Laboratory Medicine and the University Setting	161
5.4.	The Rise of Surgery in Britain and its Importance for the Changing Concept of Disease	165
5.5.	From the Laboratory to the Clinic and <i>Vice Versa</i>	169
5.6.	Controlling Disease	172
5.7.	The Organ Replacement Concept and Competing Theories	176
5.8.	Fostering Professional Interest	181
5.9.	Conclusion	185
Chapter 6	Considering the Risk: The Ethical Dimension and the Failure of Organ Replacement Therapy in Clinical Practice	187
6.1.	Introduction	187
6.2.	Using Animal Organs	188
6.3.	The Problem of Gaining Human Thyroid Extract from the Living or Dead	191
6.4.	Patient Consent and the Problem of Human Experimentation	195
6.5.	Ethics and Organ Replacement Therapy from 1890 to 1920	201
6.6.	The Problem of Establishing Therapeutic Success: Morphological Considerations	203
6.7.	Functional Considerations	207
6.8.	The Problem of Causal Attribution	212
6.9.	Conclusion	216
	Final Conclusion	220
	Bibliography	227
	Primary Sources (Printed, Re-Printed and Archival)	227
	Secondary Sources	240
Appendix	Timeline	251

INTRODUCTION

On Friday, May 25, 1888 a crowd was filling up the small theatre at 20 Hanover Square, London, for the twenty-first season's closing session of the Clinical Society of London. Usually, attendance was sparse, with the more junior physicians being taken to task by their seniors. But this time the audience—including a delegation from the United States—waited in anticipation of a special event: the public presentation of the final report of the society's 'Committee to Investigate the Subject of Myxoedema,'¹ which was finally complete after five years of work and many a setback. There were two principal conclusions presented that day. First, that myxoedema, until then a peculiar and incurable disorder of adults with thick skin, slow speech, and diminished mental faculties, was practically identical to cretinism. Nevertheless, what really piqued the audience's interest was the second conclusion, i.e. that these symptoms were dependent upon the destruction or loss of the thyroid gland.²

These conclusions, but especially the second, were remarkable for several reasons. On the one hand because, by 1888, the thyroid gland had no known physiological function; on the other hand, cretinism was believed to be either a congenital disease, i.e. patients were born cretinoid, or, at the very least a chronic children's disease, meaning that patients suffering from cretinism never developed the condition after their 18th birthday.³ Although these certainly were clear-cut conclusions for the time, even more remarkable is that a committee, a device not generally given to clear conclusions, reached them. However, as will later be discussed in this thesis, a closer reading of the actual report shows that clarity here came at a

¹ William Miller Ord et al., *Report of a Committee of the Clinical Society of London Nominated December 14, 1883, to Investigate the Subject of Myxædema*, vol. 21 (Supplement) (London: Longmans, Green & Co., 1888).

² Ibid., 21 (Supplement):200–202.

³ Thomas Schlich has investigated the reception and changing ideas regarding cretinism for the Swiss context and found that the principal authorities on the question empirically excluded the possibility of cretinism to develop past this age; for this see Thomas Schlich, "Changing Disease Identities: Cretinism, Politics and Surgery (1844-1882)," *Medical History* 38 (1994): 421–443.

price. There appears to have been a consensus among the committee members that patched over differences, because they chose to give more weight to some data at the expense of other data, i.e. they balanced and judged clinical and experimental evidence that was not always in agreement. Most importantly, however, the prime conclusion, the loss of the thyroid gland being responsible for the onset of myxoedema, was at that time a conjecture made with neither clinical nor scientific substantiation.⁴

To an extent, these conclusions proved to be most influential for the development of three factors: firstly, the conception of myxoedema from a fuzzy ailment to a disease entity; secondly, for the development of a notion regarding the thyroid's physiological function; and thirdly, for the invention of a corresponding therapy, i.e. organ replacement therapy by means of liquefied thyroid tissue. However, the growing awareness that somehow the loss of the thyroid gland could bring about pathologic changes within the body is certainly not equivocal with the idea that the gland itself had a particular function, or that the publication of the report would mark the beginning of modern endocrinology, as some historians have argued.⁵ But without the acceptance, or at least an authoritatively substantiated dissemination of the idea of thyroid dysfunction, the developments of the 1890s, during which clinicians and medical scientists alike began to successfully experiment with thyroid replacement therapy, would hardly have been possible.⁶ The very idea of endocrine organ

⁴ The causal link between myxoedema and the thyroid gland proposed in the *Report*, although appearing in the final conclusion, was not uncontested by the committee members themselves. It was an addition made due to the failure of proving any connection between myxoedema and a pathological accumulation of mucus (*mucin*) in the lower layers of the skin (*oedema*), which gave the condition its original name *myxoedema (mucin-oedema)*.

⁵ Diana Long Hall and Thomas F Glick, "Endocrinology: a Brief Introduction," *Journal of the History of Biology* 9 (1976): 229–233; Clark T. Sawin, "The Invention of Thyroid Therapy in the Late Nineteenth Century," *The Endocrinologist* 11 (2001): 1–3; P.M.F. Bishop, "The Development of British Endocrinology," *British Medical Journal* (1955): 866–870; A F Hughes and Margaret Wells Egar, "A History of Endocrinology," *Journal of the History of Medicine and Allied Sciences* 32 (1977): 292–313; Humphry Rolleston, "Endocrines in Theory and Practice: The History of Endocrinology," *British Medical Journal* 1 (1937): 1033–1036.

⁶ For a basic historical overview, see Merrilely Elaine Borell, "Origins of the Hormone Concept" (PhD Thesis, Yale University, 1976), 68–73.

replacement therapy, as instantiated here by the example of the thyroid gland, rests on a much more complex historical framework than just the acceptance of a possibility. To better understand some of the underlying complexities, it is well-worth the effort to initially investigate some fundamental issues surrounding the historicity of the concept of organ replacement therapy and thyroid studies.

CONTEXTUALISING ORGAN REPLACEMENT THERAPY AND THYROID STUDIES

In April 1891, the French neurologist and physiologist Charles Eduard Brown-Séquard (1817–1894) and his assistant Arsène d’Arsonval (1851–1940) suggested to the Parisian Society of Biology that potent substances, which they called *internal secretions*, existed in the tissues of animal organs, and that certain kinds of internal diseases probably resulted from a deficiency or lack thereof. The duo presented to their colleagues that one might discover these substances by using extracts gained from tissue samples to treat such diseases. They argued further that, should a given condition be successfully treated by the use of such extracts, it was likely that the condition was caused by inadequate production of internal secretion. In a brief note, they outlined a programme of experimental therapy to search for these substances.⁷

This form of organ replacement therapy had conceptually originated two years earlier in Brown-Séquard’s rejuvenation studies. At a similar meeting of the Society of Biology, he had argued that the testes probably produced a “dynamogenic” substance, which might be extracted from these organs of animals and injected into ageing or debilitating individuals to restore their vigour and strength. Brown-Séquard based his argument for pursuing these experiments on commonly accepted assumptions about human sexuality. For example, it was

⁷ Charles-Éduard Brown-Séquard and Arsenne d’ Arsonval, “De l’injection des extraits liquides provenant des glandes et des tissus de l’organisme comme method thérapeutique,” *Comptes rendus de la Société de Biologie* 9 (1891): 248–250.

widely held that the loss of semen resulted in the loss of physical strength and mental agility, and that indulging in masturbation led to debility. Brown-Séquard argued that the retention of semen ought to combat these degenerative effects. Furthermore, he suggested that the testes produced a substance which was nutritive to the nerves, and which might be extracted. In the light of these arguments, many physicians proved to be willing to test his ideas, and the so-called Brown-Séquard-Fluid came to be tried in the treatment of a variety of nervous and debilitating conditions. This mode of therapy became popular not only in France, but also in the United States and Russia. By spring 1891, a number of investigators had realised that similarly potent medicaments might be extracted from other tissues, and physicians in Paris were asking Brown-Séquard to provide them with these preparations.

A therapy “which aims at replacing an organ that has lost its function in the organism” is nothing to be made light of, the surgeon Victor Horsley (1857–1916) warned his colleagues in 1892.⁸ Today, no one would earnestly doubt the seriousness of a medical doctor who treats a disease by replacing an organ’s function. To us it may seem self-evident that certain internal diseases result from the failure of a particular organ, and that it makes medical sense to treat patients by replacing that organ’s function. This is why it may come as a surprise that before the late 1880s no one had even considered treating internal diseases using such an approach. Yet, organ replacement therapy, together with the corresponding assumptions about the nature of the body and disease, did not arise before the period from 1880 to 1900. There was no such thing as a long-held desire of the medical profession about organ replacement therapy.

At this point, a definition is called for: this thesis deals with organ replacement therapy as it is carried out today under the name of “hormone replacement therapy” for the pancreas or the

⁸ Victor Alexander Hayden Horsley, “Remarks on the Function of the Thyroid Gland: a Critical and Historical Review,” *British Medical Journal* no. 1 (1892): 215.

thyroid gland. In order to effectively treat diseases such as diabetes or hypothyroidism, the function of the corresponding organ is replaced by administering the hormones insulin or thyroxin respectively. Organ replacement therapy in this sense thus differs fundamentally from organ transplantations, where a surgeon transplants an organ or organ tissue into the body where it continues to live and function, or plastic surgery, where damaged parts of the body's surface are replaced. The latter process has been performed for centuries and falls within the traditional purview of surgery. From the perspective of organ replacement therapy, the crucial innovation was to apply this already existing approach to interior functions of the body's organs and thus to the treatment of internal diseases.⁹ Contemporary writers were already aware that "the replacement of function of organs that are degenerated or do not work for other reasons" constituted a particular and novel field of enquiry.¹⁰ Until about 1914 the new therapeutic concept boomed. "We are today in an era that is capable of replacing organ functions," a physician commented in 1913.¹¹ At the time, however, the rise of organ replacement therapy was already turning into a decline, and by the following year, the approach had been almost completely abandoned. Experience gained during the preceding decades led to the general opinion that organ replacement therapy was not feasible because of practical problems, while the conviction that the practice was in principle an ideal therapy remained unaffected.

During the years 1880 to 1914, something happened that may be called the "invention" of organ replacement therapy. Organ replacement therapy could not be "discovered," as it did not exist before the 1880s. Neither did it "develop" by itself, driven by inherent necessities,

⁹ Which of these steps is considered new depends on the researcher's interest; see: Ilana Löwy, *Medicine and Change: Historical and Sociological Studies of Medical Innovation* (Paris: John Libbey, 1993), 3–4.

¹⁰ Victor Alexander Hayden Horsley, "Experimental and Clinical Contributions of Thyroid Tissue Replacement," *International Clinics* 16 (1906): 151.

¹¹ Frederick M. Allen, *Studies Concerning Myxoedema* (Cambridge, Mass.: Harvard University Press, 1913), 5.

medical progress, or the spirit of the times. It had to be “invented.” As an invention, organ replacement therapy was the result of a particular human activity at a particular time, dependent upon particular technological, social, and cultural conditions.¹²

The term “invention” designates a complex process extending over a period of time. Organ replacement therapy and its theoretical basis were not invented by one person in a single, complete act of invention; rather, there was a “process of invention” involving a number of inventors. In any case, it would not have sufficed for the new therapy to have been invented by one person in one place; rather, innovations of this kind gain significance from their reception, from being taken up by interested doctors and scientists. In the course of its reception, the concept of organ replacement therapy and its respective forms of application were modified. Its reception was thus a part of the invention process and established the usefulness of what had been invented. An innovation never spreads on its own; it is always necessary to convince others that it is worth adopting. In a way, the “demand” for the new therapeutic method was invented along with it. This is not to deny that organ replacement therapy was a beneficial technique. However, for this to become the case, medical reality had to be structured and perceived in a particular way, i.e. the act of perceiving the body had to be—at least fragmentarily—reconfigured. In this thesis, I aim to unravel this restructuring and reconfiguration to elucidate the changes, both epistemic and practical, that accompanied the introduction and invention of this novel technique with regard to the thyroid gland. For my purposes, the crucial criterion is the historical actors’ own assessment of what it was that they did. These assessments provided the basis for both the initial success and the later decline of organ replacement therapy.

¹² See Andrew Cunningham, “Identifying Disease in the Past: Cutting the Gordian Knot,” *Asclepio* 56 (2002): 16.

With the introduction of the hormone concept in 1905, the chemical coordination of physiological processes was recognised as a new phenomenon for biological investigations.¹³ Between 1889 and 1905, the issues motivating investigators had been gradually transformed. The changing concerns and perceptions of investigators at this time derived, in part, from the institutional setting in which the problems relating to internal secretions were first raised. Consequently, I have concentrated my efforts on understanding the nature of the problems that investigators were trying to solve. In so doing, I have had to re-evaluate what these investigators saw as their primary research goals and determine how they perceived the novelty which was, in fact, an innovation. Whilst in the French context, the essential innovation in this period was the creation of an awareness of internal secretions in animal tissues; in Britain, the innovation was the creation of an awareness that these discrete chemical substances could, just like nervous stimuli, trigger certain physiological and pathological events.

I have, for the most part, ignored the responses to these developments in the German-speaking countries, because historical witnesses maintained that there was limited interest in the problem of internal secretion in those countries until the second decade of the twentieth century, at which time there was no question of the potential significance of this line of investigation.¹⁴ The experiments of Arnold Berthold (1803–1861) in Germany on caponisation, i.e. the sterilisation of roosters, and testicular grafts were then, like the experiments of Gregor Mendel on the genetics of peas, rediscovered. Investigators working on highly

¹³ For a more recent analysis of the impact of the hormone concept see: Jens H Hendriksen, *Starling, His Contemporaries and the Nobel Prize: One Hundred Years with Hormones* (Oslo: Taylor and Francis, 2003). Borell, however, discusses the invention of hormones by Starling as well, see: Borell, "Origins of the Hormone Concept," 131–144.

¹⁴ See Artur Biedl, *The Internal Secretory Organs: Their Physiology and Pathology* (New York: William Wood, 1913), 3–5. Biedl reports that "German physiologists and clinicians were extremely sceptical of Brown-Séquard's theories." Although David Paul von Hansemann (1858–1920) of Berlin also developed a theory of "cell altruism" which emphasised functional independence among cells, Biedle credits Brown-Séquard with opening "to physiology a new and fruitful field for experiment," paving "the way for the right understanding of many pathological derangements," and pointing out "a rational and, in many cases, a remarkably successful method of treatment."

specialised problems in physiology seemed to be quite frankly embarrassed that the fundamental questions regarding the chemical control of physiological processes had been overlooked for so long.

In both France and Britain, the close association of clinical and physiological research was an important influence on the responsiveness of investigators to these new ideas. In Germany, the highly professionalised pathologists and experimental physiologists worked in institutes that were usually separated from the clinic.¹⁵ In France and Britain, however, the concerns of physicians and physiologists were usually intertwined. In this latter setting, the highly speculative ideas of Brown-Séquard were not overlooked or dismissed *per se*, at least not completely, as I will discuss later in this thesis. The complexities of clinical problems made his ideas at least feasible. Moreover, his speculations seemed to order a variety of unexplained observations. The question remained how to test these ideas most effectively. It is towards the resolution of these strategic problems that much of my discussion is aimed at. In this case, the questions raised by clinical concerns could be answered by the application of laboratory techniques in experimental physiology. In the process of solving these problems, new domains were opened to medical science.

Since, in the particular case of thyroid endocrinology, a fundamental biological problem was raised in direct response to a specific problem in medicine, it is legitimate to question whether the 'struggle for independence' enriched or constrained nineteenth-century

¹⁵ Ben-David provides a general overview of the growth of German science during the nineteenth century: Joseph Ben-David, *The Scientist's Role in Society: a Comparative Study* (Englewood Cliffs, N.J.: Prentice-Hall, 1971), 108–138. For a discussion on the growth and establishment of physiology, see: A. Zloczower, "Career Opportunities and the Growth of Scientific Discovery in 19th Century Germany with Special Reference to Physiology" (The Hebrew University of Jerusalem, 1966); Arleen Marcia Tuchman, *Science, Medicine, and the State in Germany: The Case of Baden, 1815-1871* (Oxford: Oxford University Press, 1993). Eulner lists the German institutes of physiology: Hans-Heinz Eulner, *Die Entwicklung der Medizinischen Spezialfächer an den Universitäten des Deutschen Sprachgebietes* (Stuttgart: Ferdinand Enke, 1970), 63.

physiology.¹⁶ The invention of organ replacement therapy in response to the changing nature of thyroid physiology and pathology must be viewed as a result of a conjunction of ideas rather than the logical outcome of any specific technical or conceptual advance in physiology. This conjunction of ideas resulted from a focus on many traditional lines of research—clinical medicine, surgery, pathology, histology, neurology, and physiology—applied onto a specific group of biological phenomena which were related to an unexplored organ: the thyroid gland. Further investigations of the function of this organ became necessary after 1891, due to the widespread acceptance of the belief that the body's tissues probably produced highly potent, physiologically active substances, which were necessary for the regulation of normal biological processes. This belief led to the expectation of clinicians and medical scientists that these substances could be harvested from the organs and utilised in clinical care and laboratory research. In this thesis, I describe not only the search for one of these substances but also the implications of the struggle, success, and failure of that search for the directions of late-Victorian medical science.

The details of this search for the internal secretion of the thyroid gland were particularly important for altering developments in the field of endocrinology because of the historical context in which the notion of internal secretions was first raised. The general recognition of the existence of potent substances in animal tissues derived largely from an interest in Brown-Séquard's rejuvenation experiments, the supporting logic for which he had developed from nineteenth-century ideas about human sexuality. Brown-Séquard's ideas came to be elaborated and exploited by medical scientists and charlatans alike. As a consequence, professional legitimacy emerged as a major concern to investigators in this field. By the turn of the century, intense debate over legitimate techniques, strategies, and the domain of the

¹⁶ J. Schiller, "Physiology's Struggle for Independence in the First Half of the Nineteenth Century," *History of Science* 7 (1968): 260–270.

research field flared up in the pages of leading medical journals.¹⁷ Physicians, physiologists, and chemists argued over the proper methods of investigation, while at the same time, the pharmaceutical market was flooded with preparations of animal extracts of often dubious therapeutic value. The sources of these debates and the enthusiasm for organ extracts as therapeutic agents may be traced back to the redefinition of myxoedema between 1878 and 1888 and the subsequent development and dissemination of thyroid replacement therapy from 1891 onwards.

It is part of the purpose of this thesis to describe how British physiologists and clinicians came to recognise that internal secretions exist in animal tissues and to examine how they learned to evaluate and utilise the effects of these substances. The demonstration of a therapeutically active thyroid extract resulted in the exploration of new physiological problems, which, over the next decade, became the focus of the emerging field of endocrinology.

THE DE-HISTORISATION OF ORGAN REPLACEMENT THERAPY

Contrary to the aims just indicated, previous historiography has largely de-historicised organ replacement therapy. Most of the articles and books on the subject have been written not by historians but by medical specialists themselves. As a rule they proceed from the assumption that organ replacement therapy was one of medicine's most wished-for desires and that the reason why doctors were anxious to put it into practice are somehow self-evident.¹⁸

¹⁷ For commentaries on the state of the field at the founding of the Association of the Study of Internal Secretions in 1917, see: Frederick G. Hoffman, "The Fifth Anniversary," *Endocrinology* 80 (1967): 1–4; Hans Lisser, "The Endocrine Society: The First Forty Years (1917-1957)," *Endocrinology* 80 (1967): 5–28. For a brief discussion of the "crisis of confidence in endocrinology," see: Diana Long Hall, "Biology, Sex Hormones and Sexism in the 1920's," *Philosophical Quarterly* 5 (1973): 84.

¹⁸ Among the early endocrinologists, Humphry Rolleston, for example, liked to cultivate the identity of his field as having a very long history, claiming he put medieval dreams into practice; see Humphry Davy Rolleston, *The Endocrine Organs in Health and Disease with an Historical Review* (Oxford: Oxford University Press, 1936), x–xi. On this self-perception of early endocrinologists see also Susan E Lederer, *Flesh and Blood: Organ Transplantation and Blood Transfusion* (New York: Oxford University Press, 2008), 20–21.

In the very beginning, the scientific and medical community was still conscious of the novelty of organ replacement therapy. As mentioned above, Victor Horsley felt he had to admonish his colleagues to acknowledge organ replacement therapy as a serious subject. In 1897, he traced the idea of organ replacement therapy no further back than Brown-Séquard's experiments performed only ten years earlier. As late as 1919, thyroid research of the 1880s was still conceived of as the starting point for the organ replacement therapy concept and was defined as separate from earlier, only superficially similar activities.¹⁹ Nevertheless, the more the new approach became established, the more it became de-historicised: in 1914, the Swiss surgeon Theodor Kocher (1841–1917) ignored his own initial doubts about whether this procedure made any medical sense and declared that the concept had been obvious from the beginning.²⁰ Since then organ replacement therapy has frequently been characterised as a procedure that has always been logical and self-evident.²¹ After 1920, doctors began to refer to it as one of the holy grails of medicine.²² Now that the concept had been established, the retrospective impression was that this had always been the case.

Up to the present time, most of the writings on this subject shared this point of view, implicitly or explicitly. Referring back to ancient mythology, or medieval hagiography, authors reinterpreted a whole range of different cultural traditions as pertaining to the organ

¹⁹ Ernest W. Hey Groves and Cecil Joll, "Thyroid and Its Treatment," *British Medical Journal* no. 2 (1919): 1965.

²⁰ Theodor E. Kocher, "Über die Bedingungen erfolgreicher Schilddrüsenimplantation beim Menschen," *Verhandlungen der Deutschen Gesellschaft für Chirurgie* 43 (1914): 486.

²¹ Jerome John Logan, "Surgical Thyroid Disease," *British Medical Journal* no. 2 (1916): 995–996; Malcolm Storer, "On Thyroid Replacement," *Boston Medical and Surgical Journal* 172 (1915): 41–46; Henry R. Harrower, *Outlines of Organotherapy* (Glendale, Cal.: Self-published, 1918), 13–14.

²² L. L. Stanley, "An Analysis of One Thousand Thyroidal Substance Implantations," *Endocrinology* 6 (1922): 787; William S Bainbridge, "Treatment with Human Thyroid Extract: Present Status and Future Possibilities," *American Journal of Obstetrics and Gynaecology* 5 (1923): 495; Edward Sharpey-Schäfer, *History of the Physiological Society During Its First Fifty Years, 1876-1926*, Issued by the Society and Published as a Supplement to the Journal of Physiology (London: Cambridge University Press, 1927), 112.

replacement concept.²³ These accounts do not even begin to discuss the appropriateness of their interpretation.²⁴ They simply take it for granted that the historical sources they have used are reports of organ replacements in the modern sense. As a result, organ replacement therapy invariably appears as if it had always existed, at least as a concept.²⁵ The question of when and how the concept arose therefore rarely comes up. In his popularising account of the history of organ replacement therapy, the physician Francis Moore claimed that organ replacement therapy was “a medical development awaited and anticipated for centuries.”²⁶ Any relation to place, time, culture, or particular processes of invention has been “written-out” of the story here, bestowing on the practice of organ replacement therapy an aura of self-evidence and inevitability that makes it almost impervious to critical discussion.

Promoting organ replacement therapy is one clearly identifiable aim of most of its historiographical accounts. This in itself is by no means dishonourable; however, the results of this kind of historiography contradict both the research interests and methodological standards of serious historical analysis—not that serious historical research could not benefit from reviews written by medical practitioners. Thus, for instance, Michael Woodruff’s voluminous book on the replacement therapy of tissues and organs published in 1960, containing numerous reviews and thousands of references, is an excellent basis for any

²³ David Hamilton, *A History of Organ Transplantation: Ancient Legends to Modern Medicine* (Pittsburgh: University of Pittsburgh Press, 2012); A.M. Ahmed and N.H. Ahmed, “History of Disorders of Thyroid Dysfunction,” *Eastern Mediterranean Health Journal* 11 (2005): 459–469; Franz Merke, *History and Iconography of Endemic Goitre and Cretinism* (Lancaster: MTP Press, 1984); Vasilli Leoutsakos, “A Short History of the Thyroid Gland,” *Hormones* 3 (2004): 268–271; T. Lee, “A Brief History of the Endocrine Disorders in China,” *Chinese Medical Journal* 59 (1941): 379–386; Hughes and Egar, “A History of Endocrinology.”

²⁴ This and the following statements apply to the history of organ replacement therapy. It has to be noted that in 2010, Thomas Schlich has made very similar remarks about the history of organ transplantation and, accordingly, attempted to rectify these shortcomings. See: Thomas Schlich, *The Origins of Organ Transplantation: Surgery and Laboratory Science, 1880-1930* (Rochester, NY: Rochester University Press, 2010).

²⁵ For an analogous idea in the history of science, see Steve Woolgar, *Science: The Very Idea* (London: Tavistock, 1988), 53–82.

²⁶ Francis D. Moore, *Give and Take: The Development of Tissue Transplantation* (Philadelphia: Saunders, 1964), vi.

research into the technical history of this procedure.²⁷ The type of information found in Woodruff's book is also what many accounts by medical historians have to offer. These writings scarcely differ from those of medical practitioners, and can also be placed in this category.²⁸ Witness reports²⁹ and biographies³⁰ also have great documentary value. They reflect the participants' perspectives and convey opinions, views, and connections that cannot be found in other sources. All of these historical accounts, however, represent a special kind of source materials rather than contributions to a serious case history of organ replacement therapy, as based, for example, on the thyroid gland and myxoedema.

The fact that there was an actual beginning to the idea of organ replacement, and that the concept and the practice have to be looked at as historical phenomena, has been the subject of only one historical investigation to date. Merriley Borell's doctoral thesis from 1976, however, has almost exclusively focussed on the immediate context of the dissemination of Brown-Séquard's ideas in France.³¹ Those historical accounts that deal with the therapies and concepts relating to sex hormones have largely omitted this point, as it bears little relevance to their subject.³² The same applies to studies that do not deal directly with the concept and

²⁷ Michael F. A Woodruff, *The Transplantation of Tissues and Organs* (Springfield, IL: Thomas, 1960).

²⁸ Hamilton, *A History of Organ Transplantation: Ancient Legends to Modern Medicine*; David Hamilton, *The Monkey Gland Affair* (London: Chatto & Windus, 1986); J. Dadan and A. Nowacka, "A Journey into the Past: The History of Thyroid Surgery," *Wiadomości Lekarski* 61 (2008): 88–92; Hughes and Egar, "A History of Endocrinology"; *The Cambridge World History of Human Disease* (Cambridge: Cambridge University Press, 1993); Peter Langer, "History of Goitre," *World Health Organization Monograph Series* 44 (1960): 9–26; Victor Cornelius Medvei, *The History of Clinical Endocrinology: A Comprehensive Account of Endocrinology from Earliest Times to the Present Day* (Carnforth: Parthenon, 1993); S.T. Logan and J.S. Logan, "The Treatment of Myxoedema with Raw Sheep Thyroid Gland and Its Introduction into Practice in County Londonderry in 1892," *The Ulster Medical Journal* 61 (1992): 86–93.

²⁹ George Redmayne Murray, "The Life-History of the First Case of Myxoedema Treated by Thyroid Extract," *British Medical Journal* 1 (1920): 334–335.

³⁰ Stephen Paget, *Sir Victor Horsley* (New York, 1920).

³¹ Borell, "Origins of the Hormone Concept."

³² Nelly Oudshoorn, *Beyond the Natural Body: an Archeology of Sex Hormones* (London: Routledge, 1994); Chandak Sengoopta, *The Most Secret Quintessence of Life: Sex, Glands, and Hormones, 1850-1950* (Chicago: University of Chicago Press, 2006); Helga Satzinger, *Differenz und Vererbung: Geschlechterordnungen in der Genetik und Hormonforschung 1890-1950* (Köln: Böhlau, 2008); Elizabeth Siegel-Watkins, *The Estrogen Elixir: a History of Hormone Replacement Therapy in America* (Baltimore: Johns Hopkins University Press, 2007).

practice of organ replacement therapy, such as the origin of utilised organs and the history of organ donation.³³ Furthermore, some historical accounts restrict themselves to the period of the 1950s onwards.³⁴ It seems to have been forgotten that a great number of papers and books on organ replacement therapy were published between the 1880s and 1910s, and that hundreds of these procedures have been performed during that time. This disregard for the entire foundational period of organ replacement therapy represents another instance of the tacit assumption that this therapeutic method has always been in existence, at least as an ideal or an idea.

As sociological studies are limited to the (respective) present, they do not make up for this deficiency either.³⁵ Nor do dissemination studies pursue the question of the “invention” of organ replacement therapy. Titles such as *Organ Replacement Therapy: New Advances in an Ancient Method* reveal the implicit assumption that the practice spread more or less by itself, as long as it was not impeded by extraneous factors such as politics, culture, or legislation, because it is based on an ahistorical and self-evident rationality.³⁶ From this point of view, the idea and the practice of organ replacement therapy have no describable origin either.

So far, except for Borell’s study of Brown-Séquard’s immediate discovery and Thomas Schlich’s book on the history of organ transplantation in the (mostly) German-speaking countries, there has been no systematic study of the early phase of organ replacement

³³ Kieran J Healy, *Last Best Gift: Altruism and the Market for Human Blood and Organs* (Chicago: University of Chicago Press, 2006); Lesley Sharp, *Strange Harvest: Denatured Bodies and the Transformed Self* (Berkeley, Los Angeles: University of California Press, 2006).

³⁴ Leoutsakos, “A Short History of the Thyroid Gland”; A. P. Cawadias, “The History of Endocrinology,” *Proceedings of the Royal Society of Medicine* 34 (1940): 25–30.

³⁵ The sociologist Renée Fox and the biologist Judith Swazey traced the developments of hormone replacement therapy after World War II and described the interaction between doctors and patients, scientists and politicians in their 1974 study Renée C Fox and Judith P Swazey, *The Courage to Fail: A Social View of Organ Replacement and Dialysis* (Chicago: Chicago University Press, 1974). For a more recent assessment by the same authors, see: Renée C Fox and Judith P Swazey, *Spare Parts: Organ Replacement in American Society* (New York: Oxford University Press, 1992).

³⁶ Michael A Bos, *Organ Replacement Therapy: New Advances in an Ancient Method* (London: King’s Fund Centre, 1991).

therapy and its ramifications for the conceptions of disease and illness, especially for the Anglophone context. Scattered references to some early cases do not correct the overall picture.³⁷ Thus, the question of what constituted the new step toward organ replacement therapy has not arisen. The same is true for the way the approach is dealt with in the context of other medical fields and technologies, such as the history of immunology, say. Here, too, the implicit assumption is that it is and always has been desirable to use organs as therapeutic means to combat internal diseases.³⁸

Considering the overall literature, it is apparent that there is still no history of the early phase of organ replacement therapy for the British context that counteracts the prevalent de-historicisation of the subject. The historiography of medicine and science has not yet produced a serious and extensive study on this subject. Apart from the context of sex hormones, for which the historical starting point lies well within the twentieth century, historians have largely ignored its history. Historical research's relative indifference is all the more remarkable considering its general significance for related historical subjects. One would assume that historians' increasing interest in the body, for example, would be a reason to focus on this kind of intervention into the interior of the body, with its corresponding concepts and representations of the body. Yet, it has so far failed to become a popular topic for historical studies. Apart from the notable exception of the history of sex hormones and women's history, historical research seems to take such concepts for granted. Thus, historians

³⁷ L. Doyle, "Myxoedema: Some Early Reports and Contributions by British Authors, 1873-1898," *Journal of the Royal Society of Medicine* 84 (1991): 103-106; Logan and Logan, "The Treatment of Myxoedema with Raw Sheep Thyroid Gland and Its Introduction into Practice in County Londonderry in 1892"; James N. Parker and Philip M. Parker, *Myxoedema: A Medical Dictionary, Bibliography, and Annotated Research Guide to Internet References* (San Diego, CA: Icon, 2004); Emily Banks, "From Dogs' Testicles to Mares' Urine: The Origins and Contemporary Use of Hormonal Therapy for the Menopause," *Feminist Review* (2002): 2-25; Kent Holtdorf, *Hormone Replacement Therapy and the Biodental Debate: Are They Really Safer and More Effective Than Synthetic Hormones?* (Today Radio, 2010).

³⁸ Arthur M Silverstein, *A History of Immunology* (San Diego: Academic Press, 1989).

usually accept the physiological or pathological knowledge that provides the conceptual basis as an unproblematic given.

POINTS OF DEPARTURE FOR A HISTORICAL CONSIDERATION

Sociologists and cultural anthropologists have taught historians of medicine that concepts of illness and health in general as well as the classifications and notions of individual diseases in particular have no universal validity; indeed, that they need not even necessarily be seen as more or less successful approximations of objective reality but as varying constructs depending on their context.³⁹ From this perspective, historians have described certain aspects of medical knowledge and practice, such as disease concepts, as socially and historically constructed.⁴⁰ Modern science-based medicine, however, has mostly been excluded from such considerations. Instead, the focus has been on the superseded knowledge of the past or on 'soft' facts, that is concepts and practices that are obviously influenced by culture and society, for example in psychiatry. By contrast, the proponents of 'science and technology studies' (STS) have challenged the claim of modern science to represent and shape reality independent of any cultural or social influences. Applied to the history of medicine, STS approaches can make even the laboratory sciences, physiology, and other constituents of the hard core of modern medicine accessible for truly historical analysis.⁴¹

³⁹ Jens Lachmund and Gunnar Stollberg, eds., *The Social Construction of Illness: Illness and Medical Knowledge in Past and Present* (Stuttgart: Steiner, 1992); Charles E. Rosenberg et al., eds., *Framing Disease: Studies in Cultural History* (New Brunswick: Rutgers University Press, 1992); Ilana Löwy, "Medicine and Change," in *Medicine and Change: Historical and Sociological Studies of Medical Innovation*, ed. Ilana Löwy (Paris: John Libbey, 1993), 1–20.

⁴⁰ See Peter Wright and Andrew Treacher, eds., *The Problem of Medical Knowledge: Examining the Social Construction of Medicine* (Edinburgh: Edinburgh University Press, 1982). See also Rosenberg et al., *Framing Disease*. In addition, passages in Lachmund and Stollberg, *The Social Construction of Illness: Illness and Medical Knowledge in Past and Present*. Here especially the editors' introduction. For a survey, see Ludmilla Jordanova, *Sexual Visions: Images of Gender in Science and Medicine Between the Eighteenth and Twentieth Centuries* (Madison: University of Wisconsin Press, 1989).

⁴¹ Bruno Latour, *The Pasteurization of France* (Cambridge, Mass.: Harvard University Press, 1988); Andrew Cunningham and Perry Williams, *The Laboratory Revolution in Medicine* (Cambridge: Cambridge University Press, 1992); Ludmilla Jordanova, "The Social Construction of Medical Knowledge," *Social History of Medicine* 8 (1995): 361–381.

Historians of medicine have not yet made full use of this opportunity. On the contrary, the turn toward hitherto neglected subjects—the history of alternative medicine, non-academic medical practitioners, midwives, or patients, for example—has made the study of the traditional topics of medical history, such as victorious concepts and their historical proponents, increasingly unattractive. Of those historians who have considered themselves critical, the majority has not been interested in the technical content of medical knowledge and practice, or the dynamics and conceptual changes of the biomedical sciences.⁴² As a consequence, precisely those ideas and practices that have the greatest influence on our lives have remained outside the focus of historical consideration.

Physicians, surgeons, and physiologists, however, have not been totally excluded from recent historiography. What has been studied, though, is mostly their social aspects, such as the history of physiologists or surgeons as a professional group in the general context of professionalization in medicine. What these doctors actually did in their work has been almost completely disregarded, so much so that, in the end, it is of secondary importance whether these practitioners have been examined or some other occupational group is being dealt with.⁴³ Just as the traditional history of medicine more or less represented a sort of technological determinism, which ascribed the rise and success of modern medicine to the expansion of its technological means, so social history has tended towards a social determinism which assumes that doctors were able to extend their field of activity to the interior of the body by virtue of their changing, or in the case of surgery, newly acquired social

⁴² John Harley Warner speaks of a deligitimisation of such topics. See John Harley Warner, "The History of Science and the Sciences of Medicine," *Osiris* 10 (1995): 173. There are, of course, exceptions; see, among others, Christopher Lawrence, "Democratic, Divine, and Heroic: The History and Historiography of Surgery," in *Medical Theory and Surgical Practice: Studies in the History of Surgery*, The Wellcome Institute Series in the History of Medicine (London: Routledge, 1992); Löwy, "Medicine and Change"; William F Bynum, *Science and the Practice of Medicine in the Nineteenth Century* (Cambridge: Cambridge University Press, 1994).

⁴³ For example see Lawrence, "Democratic, Divine, and Heroic: The History and Historiography of Surgery," 13–16; John E Lesch, *Science and Medicine in France: The Emergence of Experimental Physiology, 1790-1855* (Cambridge, Mass.: Harvard University Press, 1984); Kathryn Montgomery, *How Doctors Think: Clinical Judgment and the Practice of Medicine* (Oxford: Oxford University Press, 2006).

status.⁴⁴ Since the investigation of the social and political aspects of medicine has been deemed of primary importance, medical knowledge itself and what actually happened at the bedside, in the operating theatre, or inside the laboratory has been relegated to the background.⁴⁵

In order to balance this bias, historical interest should be extended beyond the interactions of human beings. For it is not the social construct alone that is at issue. The materiality of objects, the clinicians' and scientists' concrete manipulations of the bodies and materials have to be part of that story, too.⁴⁶ The analysis should also include the ideas and concepts that were connected with these practices. Most historical accounts of physiologists, for example, are severely hampered by the assumption that the theory and practice of what is being studied are in a way self-evident. Yet, as Christopher Lawrence reminds us, even the simplest medical intervention must be regarded as a complex cultural phenomenon and not an unproblematic consequence of the nature of things.⁴⁷ Medical practice always contains, explicitly or implicitly, particular presuppositions, a particular view of the body and its diseases. At the same time, knowledge of the body in general is shaped by medical knowledge and clinical practice. Practices and concepts influence each other; they develop in interaction.⁴⁸ For this reason, the possibility and even desirability of medical intervention is, in a way, built into the medical knowledge of the body and its diseases. Thus, medical knowledge as such is not the only way possible to understand and describe the body; it is constituted by the respective aims and interests of its clinical as well as scientifically oriented

⁴⁴ Critical of this issue regarding surgeons is Lawrence, "Democratic, Divine, and Heroic: The History and Historiography of Surgery," 15, 23–24.

⁴⁵ Critical of this issue is Löwy, "Medicine and Change," 2.

⁴⁶ See Thomas Schlich and Ulrich Tröhler, *The Risks of Medical Innovation: Risk Perception and Assessment in Historical Context* (London & New York: Routledge, 2006).

⁴⁷ Christopher Lawrence, *Medicine in the Making of Modern Britain, 1700-1920* (London: Routledge, 1994), 13; Christopher Lawrence, "A Tale of Two Sciences: Bedside and Bench in Twentieth Century Britain," *Medical History* 43 (1999): 422.

⁴⁸ John V Pickstone, "Introduction," in *Medical Innovations in Historical Perspective*, ed. John V Pickstone (Basingstoke: Macmillan, 1992), 14.

practitioners. Hence, three thematic spheres must be taken into consideration: knowledge and its production, interpersonal relations, and the relations of people to objects (including bodies and organs).⁴⁹ Ideally, modern medicine should be examined simultaneously as a field of knowledge, a practice, a profession, and as a social, cultural, and political phenomenon.⁵⁰ This would be the *non plus ultra* nature of an extensive, and admittedly multi-disciplinary, historical research.

A perspective of this kind also changes our view of the present: we can see that modern medicine is a consequence of past events, a result of the questions asked, the practices applied, the problems pursued, and the solutions accepted. Medical problems, their solutions, the demand for particular kinds of therapy, as well as the therapies themselves have been shaped by particular people in particular historical contexts. Disease, diagnosis, and therapy are thus complex products of human agency.⁵¹ Along these lines, medical practices such as thyroid replacement therapy always involve particular choices that are not predetermined by inherent necessities. Thus, organ replacement therapy as a whole is only one of many possibilities for dealing with certain medical problems. Using thyroid replacement medicaments was the consequence of a particular historical development under specific historical conditions, and it involved choosing a very specific type of medical logic. This logic favoured the strategy of controlling life processes through an active intervention that was carried out, at least initially, by a highly specialised expert targeting a circumscribed area of the body at a time when the damage had already occurred. Furthermore, using this new therapeutic approach involved choosing a particular group of patients, namely the comparatively small number of those who can benefit from the replacement of organ

⁴⁹ John V Pickstone, "Objects and Objectives: Notes on the Material Cultures of Medicine," in *Technologies of Modern Medicine*, ed. Ghishlane Lawrence (London: Science Museum, 1994), 15.

⁵⁰ Löwy, "Medicine and Change," 1–4.

⁵¹ See Pickstone, "Introduction," 13–14.

function.⁵² Which of these choices was right and which was wrong, is not the issue here. A historical examination merely aims at situating the invention and dissemination of organ replacement therapy in time and place. It can go back in time to the point at which the choices in question were made, to a time when they were not yet seen as a naturally given reality.⁵³ It can investigate who took up which problems, methods, and theories, on which criteria their choices were based, and how such decisions became accepted—in short, how a certain part of medical reality was created.⁵⁴

The present thesis necessarily encompasses only a part of medical and historical reality. The invention of organ replacement therapy for the thyroid gland was certainly not everyday medicine. It belonged to the seemingly rather cryptic sphere of activity of a group of elite scientists and medical practitioners participating in a particular medical research culture. They used specialised articles, reports, and books to communicate with each other. No university physician or medical scientist left an interesting and novel operation or observation unpublished for long. These publications are therefore the most obvious sources to draw upon.⁵⁵

In addition to these writings, the following parameters define the limits of the present thesis. The reception of organ replacement therapy outside medicine is not considered, even though, replacement therapy was, in fact, a popular topic beyond specialist literature.⁵⁶ General

⁵² A “patient elite” as the historian of science Georges Canguilhem put it, see Georges Canguilhem, *The Normal and the Pathological* (New York: Zone Books, 1989), 189.

⁵³ An important work about historians’ and sociologists’ interest in the construction of scientific reality was Bruno Latour and Steve Woolgar, *The Social Construction of Scientific Facts* (Beverly Hills: Sage Publications, 1979). For medical scientific reality, see Wright and Treacher, *The Problem of Medical Knowledge: Examining the Social Construction of Medicine*.

⁵⁴ John V Pickstone, *Ways of Knowing: a History of Science, Technology and Medicine* (Manchester: Manchester University Press, 2000), 19–25.

⁵⁵ For physiology, see John V Pickstone, “The Biographical and the Analytical: Towards a Historical Model of Science and Practice in Modern Medicine,” in *Medicine and Change: Historical and Sociological Studies of Medical Innovation*, ed. Ilana Löwy (Paris: John Libbey, 1993), 36.

⁵⁶ For the more popular perception see Lederer, *Flesh and Blood: Organ Transplantation and Blood Transfusion*.

interest in replacement therapy found expression in the public press, even in popular stories and novels, and sources of this kind could provide the basis of another study. The discussion of ethical problems arising from the procedure, especially during the early phase regarding the question of harvesting the necessary organs, is dealt with only insofar as it is reflected in the medical and scientific literature of the time. Likewise, the topic of gender identity of patients, a question surrounding the issue of using male organs on female patients, and *vice versa*, is not considered in this thesis. Finally, the present study leaves room for a more detailed discussion and analysis of the failure of the practical application of organ replacement therapy. Also beyond the scope of this investigation are the various interactions among the disciplines of immunology, genetics, endocrinology, and surgery, together with their respective research programmes. Nevertheless, this thesis will provide a new basis for further research into the above aspects and a large number of related subjects.

RATIONALE AND THESIS STRUCTURE

In order to engage with the history of the organ replacement therapy concept in a way that comes close to the one outlined above, it is necessary to focus the discussion on particulars. Overall, organ replacement therapy is too broad a concept for it to be the focus of a single study, especially considering the scope of the ramifications it had for different medical and scientific fields, its impact on society, and the issues, professional, ethical or otherwise that were conjured up in its wake. In order to avoid an unfocussed discussion, this thesis examines organ replacement therapy exclusively for the thyroid gland. Since the invention of organ replacement therapy originated in research on the thyroid gland, this organ is of special interest because it became the paradigmatic organ for this new therapeutic approach, and served as a foundation from which the principle of organ replacement was applied to other organs and tissues.

For this reason I have opted for a topical organisation for the narrative in this thesis rather than a chronological one because the complexities of the process of invention of thyroid replacement therapy largely prevent a sequential presentation of events without substantial backtracking in the narrative. The development of ideas regarding the thyroid gland, its physiology and pathology, need to be discussed separately from the disease entities of goitre, cretinism, and myxoedema in order to paint a meaningful picture of their historical development. Although interconnected processes, a strictly chronological account is in danger of falling short of elucidating the complexities of the process of invention. As stated above, I aim to unravel the process of restructuring and reconfiguration of medical reality pertinent to the introduction of organ replacement therapy in order to elucidate the changes that accompanied this novel technique. In order to structure this topical approach in a meaningful manner, I will make use of John Pickstone's constructivist historiography as presented in his *Ways of Knowing*.⁵⁷ Pickstone here talks of three 'ways of knowing' in science: 'natural history,' consisting of the description and classification of things as they were and have come to be; 'analysis' which he takes to mean the seeking of understanding by breaking these things down into their constituents; and 'experiment,' the testing with results relevant to the truth and falsity of the hypothesis or theory under investigation.⁵⁸ Pickstone's three ways of knowing, i.e. "natural history," "analysis," and "experiment" will be used programmatically, i.e. as classificatory tools to analyse the varying approaches medical doctors took to make sense of and understand the changing notions of the role of the thyroid gland and myxoedema over the course of the period under consideration. All three ways of knowing are in the tradition of 'methodological naturalism' based on the premise that all explanations must ultimately refer to objects and events in space and time on the ground that there is no non-natural order to which appeal can be made.

⁵⁷ *Ways of Knowing: A History of Science, Technology and Medicine* (Manchester: Manchester University Press, 2000).

⁵⁸ *Ibid*, 2-3.

The focus on the thyroid gland, however, needs to be further narrowed down towards the diseases which were, or would become, associated with it during the period under investigation in this thesis. The first chapter, therefore, focusses on the beginnings of an awareness of a causal link between the condition of the thyroid gland and two of the most baffling pathological conditions of the first half of the nineteenth century: goitre and cretinism. Here, I take as my focal point the ideas presented by British and Continental medical practitioners during the nineteenth century. The thyroid, although anatomically well-described, remained understudied and neglected until the early nineteenth century, and ideas regarding its function make sense only in conjunction with an in-depth discussion of theories regarding cretinism and goitre. Thus, this chapter follows a multi-angular approach: in the first part, I aim to evaluate the history of cretinism in Britain. There have been a number of proposals and descriptions of this condition, both of English and Scottish doctors that have been largely overlooked by historians of medicine. The second part directly addresses the development of the thyroid insufficiency concept. Here, I will rely heavily on the accounts of Theodor Kocher of Berne, Switzerland, who not only refined and perfected his surgical technique for the extraction of goitreous thyroid glands, but in doing so, also redefined the disease concept of cretinism and goitre as organ-based diseases. This will become especially important for the ideas presented in the following chapter about the development of myxoedema in England. This section also incorporates the change from the older endemic form of cretinism, to the newer conception, which allows for a much wider definition of this affliction. Without an engagement with Kocher's ideas, their reception, and the opposition they faced within the European medical community, any argument pertaining to the development of thyroid insufficiency will fall short of the context for most of the difficulties that clinicians and scientists encountered when attempting to disseminate their research findings and interpretations of cretinism, goitre and myxoedema.

In the second chapter, I investigate how the disease of sporadic cretinism became reassessed and reframed into the new clinical entity of myxoedema. This investigation ranges from 1878 to 1885, when the committee of the Clinical Society of London, tasked with investigating the subject of myxoedema, finished the clinical review of case reports for the disease. The final report also included laboratory analyses of animal experiments conducted to scientifically explain the associated symptoms. However, as these were not part of the clinical assessment, they will form the subject of the third chapter. This chapter also investigates the claims made by Merriley Borell, Clark Sawin, and recently by David Hamilton that the early history of myxoedema is inconsequential for an explanation of the success of the concepts of thyroid deficiency and organ replacement therapy.⁵⁹ I, on the other hand, argue that by focussing on clinical observation, this aspect of the pre-history of organ replacement therapy and myxoedema is vital for an understanding of the success of both concepts, as the results gained were seen as both reliable and accurate, thus not only helping to establish myxoedema as a clinical entity but also as a viable diagnostic tool and research topic.

In order to understand how laboratory analysis strengthened the results gained by the Committee, Chapter 3 focuses on Victor Horsley's experimental analysis of thyroid ablation in animals. This discussion is mainly based on the work carried out between 1884 and 1888, but extends its analysis to 1891 in order to investigate the wider reception and conclusions gained by Horsley and to prove the assumption of a causal link between myxoedema and the loss of thyroid function. The main aim is to try and understand how scientific analysis contributed to the concept of myxoedema but still proved insufficient for a complete understanding of the disease. It also challenges the recent assessment by historians of medicine, most notably Thomas Schlich and David Hamilton, that the rationale of attempting to prove a causal link

⁵⁹ Borell, "Origins of the Hormone Concept," 68–69; Clark T. Sawin, "Thyroid Hormone Therapy: Origins and Early History," *Thyroid Today* 13, no. 1 (1990): 2; Hamilton, *A History of Organ Transplantation: Ancient Legends to Modern Medicine*, 74.

between thyroid ablation and the occurrence of myxoedematous symptoms by way of its reversal, i.e. thyroid transplantation or grafting, was ultimately a failure.⁶⁰

Subsequently, it was not solely the results of the committee of the Clinical Society of London that demonstrated the importance of research on myxoedema to doctors and scientists at the end of the nineteenth century. Chapter 4 investigates the researches performed at the intersection of the clinic and the laboratory, including everyday medical practice. This is particularly important, as prior to myxoedema's causal attribution to the function of the thyroid, this condition was as much a mystery as any other loosely defined syndrome. Prior to the published Committee report of 1888, the disease entity of myxoedema was based on the supposedly main symptom, the accumulation of mucin in the lower layers of the patient's skin. Up to 1890, neither clinical classification nor pathological anatomy nor physiological chemistry had revealed the cause and pathogenesis of myxoedema, and pathologists had not been able to associate the condition with any identifiable lesion of a particular organ beyond reasonable doubt.⁶¹ Since the rising interest in cretinism and goitre in Britain, findings of pathological changes in the thyroid had sporadically given rise to speculations about the contribution of that organ to the pathomechanisms of these diseases and, by extension, to myxoedema during the 1880s. However, due to the prevailing ignorance regarding its physiological function, thyroid gland involvement seemed no better or worse an option than an attempt to frame myxoedema as a skin disease or as a special form of Addison's disease resulting from kidney dysfunction.⁶² None of these findings, despite the favoured but still doubted possibility of thyroidal involvement in the *Report on Myxoedema*, led to the

⁶⁰ Schlich, *The Origins of Organ Transplantation: Surgery and Laboratory Science, 1880-1930*, 57–58; Hamilton, *A History of Organ Transplantation: Ancient Legends to Modern Medicine*, 97–98.

⁶¹ William Miller Ord, "The Present State of Myxoedema: Being a Discussion of the Relevant Clinical Signs of the Disease," *British Medical Journal* 2 (1890): 1460–1461.

⁶² Abraham Lancaster, "Notes and Reflections on the Thyroid and Its Relation to Disease," *Lancet* 132 (1888): 1134–1135.

redefinition of myxoedema as an organ disease. Instead, this new definition was brought about by experimental clinical research after 1891.

This first part of Chapter 4 focuses on the development of the concept of organotherapy in France, which, in turn, was based on the physiological notion of *internal secretion*. This concept was of particular importance as it provided a medically useful framework for the clinical application of the laboratory based results discussed in the preceding chapters. This is followed by an analysis of the reception of the French ideas by the British medical community. The remainder of this chapter analyses the development of the therapeutic turning point for myxoedema based on the use of medically active preparations of liquefied thyroid glands. This therapy, which was perceived by many as the ultimate proof of the causal link between thyroid dysfunction and the onset of myxoedematous symptoms, was soon framed to be a “rational” therapy.

The first four chapters deal with the historical examination of the developing concept of organ replacement therapy as relating to the thyroid gland, applying Pickstone’s three ways of scientific knowing. We will see how the concept emerged from growing tensions between the older disease entities of endemic cretinism and goitre, and new observations in Britain that challenged fundamental assumptions about the underlying causes of these conditions as well as their pathology. Over the course of the last two chapters, I will critically examine some larger issues regarding the developments of the preceding four chapters.

Chapter 5 attributes organ replacement therapy to a particular style of medicine. The specific approach and way of reasoning involved in organ replacement therapy is summed up, characterised, and correlated with the social and professional conditions that made it possible. Besides K. Codell Carter’s concept of causal thinking in medicine the following analysis again makes use of Pickstone’s typology of medicine and science as well as some more general remarks on the periodization of clinical medicine during the late nineteenth

century. Following on from the topical historical discussion of the preceding four chapter, Carter's ideas in tandem with Pickstone's classification will provide the framework for an integrated analysis of the changing styles of medical thinking and the emancipation of the medical profession from the subjective, patient-account-centred style of practice to an analytical notion of disease and therapeutics in the (late) nineteenth century.

Pickstone's typology is an especially interesting one, as it provides a means to assess the medical profession's ability to control the newly created necessary cause for thyroid disease in particular, as well as to approach its diseases via the organ replacement concept in general. This classification will provide the framework for an analysis of changing styles of medical thinking and the emancipation of the medical profession from the subjective, patient-account-centred style of practice to an analytical notion of disease and therapeutics.

It may be argued that Pickstone's constructivist typology is at odds with Cordell Carter's realist emphasis on the importance of causal claims in the development of medical thought. However, as mentioned above, the reading of Pickstone's ways of knowing as a form of methodological naturalism grounds the discussion in a way that Carter's causal realist notion of medical explanation may be fruitfully applied. Although Carter implicitly acknowledges the superiority of experimentation as the royal road in the discovery of causal explanations, he recognises that experimental investigations are not per se able to establish causal relationships with certitude. Thus, a combination of Pickstone's constructivist notion of the development of medical thought with Carter's realist concept of causal explanation provides a usable framework for a historically sensitive analysis of the changing styles of medical thinking as outlined above.

However, organ replacement therapy was associated with questions and problems that went beyond the immediate scientific and medical domains. As a scientific and medical practice it involved the values, norms, and cultural ideas of doctors, patients and society. How closely

scientific problems were interrelated with those outside the scientific field is the focus of the last chapter. Here, I demonstrate the observation that, implicitly or explicitly, doctors and scientists concerned themselves with ethical issues even in their professional publications. Some of the problems may well connect to our modern times, for example regarding the problem of stem cell research which in itself can result in a form of replacement therapy. Such problems were in a way already discussed between the 1890s and 1920s, though not usually in relation to the concept of “medical ethics.” These materials concern above all the sources of organs used for processing into organ replacement juices, the problem of testing the new therapeutic method on humans, as well as the information and consent of the patient. I will address, discuss, and contextualise these questions in the first part of this chapter. The second part addresses the problem of determining the success of the new treatment. During the nineteenth century, the increasing scientification of medicine has resulted in a vast arsenal of laboratory equipment and tests, but also fostered the expectations of medical practitioners with regard to the objectification of clinical findings and standardisation of medical treatment. I will argue that both the ethical dimension and the determination of success with all its implications eventually hastened the disenchantment of the medical profession with the new therapy.

– CHAPTER 1 –

REDEFINING CRETINISM AND GOITRE: THE BEGINNING OF THE THYROID INSUFFICIENCY CONCEPT

1.1. INTRODUCTION

As I have laid out in the main introduction, this chapter focuses on the beginnings of an awareness of a causal link between the condition of the thyroid gland and two of the most baffling pathological conditions of the first half of the nineteenth century: goitre and cretinism. As it is often the case in the history of medical thought, conditions such as these can—at least as general ideas—be traced back to ancient times. Both Hippocrates and Galen developed their own ideas regarding glandular tissues in the human body and had their own theories as to the glands’ respective roles in pathological processes.⁶³ Therefore, in light of the then contemporary knowledge about the aetiology of endemic goitre, the condition most commonly associated with the thyroid gland, it would not seem unreasonable to infer that this disorder may have presented itself since time immemorial among the populations of various parts of the world. Indeed, it seems extremely likely that the etiological agents known today (i.e. iodine deficiency, nutritional, hygienic, and climactic factors) exercised the same influence in the distant past as they do now.⁶⁴

However, in this chapter, I take as my focal point the ideas presented by British and Continental medical practitioners during the nineteenth century. The thyroid, although well known, remained understudied and neglected until the early nineteenth century, and ideas regarding its function make sense only in conjunction with an in-depth discussion of theories

⁶³ For an overview of the respective ideas see: Vivian Nutton, *Ancient Medicine, Series of Antiquity* (London: Routledge, 2004), 23–29. 166–168.

⁶⁴ Langer, “History of Goitre,” 9.

regarding cretinism and goitre. Thus, this chapter follows a multi-angular approach: in the first part, I aim to evaluate the history of cretinism in Britain. There have been a number of proposals and descriptions of this condition, both by English and Scottish doctors that have been largely overlooked by historians of medicine.⁶⁵ Here, we will find arguments not only pertaining to the causation of cretinism and its endemic character, but also a link to politically motivated calls for reform of social conditions concerning the affected areas. The second part of this chapter addresses the development of the thyroid insufficiency concept. Here, I will rely heavily on the accounts of Theodor Kocher of Berne, who not only refined and perfected his surgical technique for the extraction of goitreous thyroid glands, but in doing so also redefined the disease concept of cretinism and goitre as organ-based diseases. This will become especially important for the ideas presented in the following chapter about the development of myxoedema in England. This section also incorporates the change from the older endemic form of cretinism to the newer conception, which allows for a much wider definition of this ancient affliction. Without an engagement with Kocher's ideas, their reception, and the opposition they faced within the European medical community, any argument pertaining to the development of thyroid insufficiency will fall short of the context for most of the difficulties both clinicians and scientists encountered when attempting to disseminate their research findings and interpretations of cretinism, goitre and myxoedema. The last section examines the problems faced by physicians and medical scientists in applying the concept of sporadic cretinism.

⁶⁵ Schlich, Medvei, Iason, Sawin, and Tröhler have focussed on the Continental ideas of cretinism. Although there is certainly a much wider and more extensive literature to be found concerning the French, Swiss, and German contexts, the British ideas do merit close inspection, especially because those ideas were the direct precursors to the later myxoedema debate.

1.2. CRETINISM

When George Redmayne Murray (1865–1939) injected a preparation of fresh sheep’s thyroid tissue under the skin of a middle-aged woman’s throat in January 1891, he performed the first “medically relevant” organ replacement therapy in the modern sense.⁶⁶ It was an operation that “generated considerable general interest,” and “hence this issue never settled down again,” as an overview put it in 1936.⁶⁷ The thyroid gland became the paradigmatic organ in early organ replacement therapy and also provided the model for most, if not all, further approaches of this kind.⁶⁸ Until the early twentieth century, it was also the most common among all organotherapeutically used organs.⁶⁹ The redefinition of a class of disorders as thyroid insufficiency diseases became the decisive step in the process that ultimately led to the creation of the hormone concept.⁷⁰ In order to historically analyse the concept of thyroid insufficiency and early organ replacement therapy, we must first turn to an earlier, non-organ-based understanding of these disease entities from which the new concept developed: cretinism and goitre. Failure to do so would result not only in a distorted picture of the historical developments both in Britain and on the Continent, but would also fall short of an understanding of the difficulties these early investigators faced in establishing their ideas regarding the function of the thyroid gland.

The diseases that were later ascribed to thyroid insufficiency had already existed in other forms that can be described as ‘disease entities,’ with the two most important being cretinism

⁶⁶ George Redmayne Murray, “Note on the Treatment of Myxoedema by Hypodermic Injections of an Extract of the Thyroid Gland of a Sheep,” *British Medical Journal* 2 (1891): 796–797.

⁶⁷ Rolleston, *Endocrine Organs*, 34; Murray, “The Life-History of the First Case of Myxoedema Treated by Thyroid Extract”; Borell, “Origins of the Hormone Concept,” 145–148.

⁶⁸ Schlich, *The Origins of Organ Transplantation: Surgery and Laboratory Science, 1880-1930*, 51.

⁶⁹ Schlich, “Changing Disease Identities”; Merrileys Elaine Borell, “Organotherapy, British Physiology, and Discovery of the Internal Secretions,” *Journal of the History of Biology* 9 (1976): 235–268.

⁷⁰ No Whiggism is intended by this statement. The analysis of the historical changes that led to this creation will be discussed in Chapter 6.

and goitre.⁷¹ A disease entity results from assigning the diseases of individual people to a specific disease designation.⁷² Looking at how disease entities changed in tandem with new treatment concepts will help identify the ways in which the novel treatment of myxoedema represented a completely novel approach to curing diseases in general and to understand the fundamental shift in disease causation that took place in the second half of the nineteenth century.

The explanation, definition, and treatment of cretinism and goitre did not at first refer to any particular organ.⁷³ An analysis of five foundational articles and a dissertation on these conditions, published between 1800 and 1855 in Britain, demonstrates the typical approach to cretinism before 1883.⁷⁴ This survey is of special interest because it may serve as a historiographical template for the understanding and conceptualisation of these diseases until the commencement of the work of the London Clinical Society's committee on myxoedema in

⁷¹ Both diseases were known since ancient times. For my reasons not to include a historical analysis of their respective history prior to the nineteenth century see the main introduction to this thesis.

⁷² The discussion about whether disease entities exist at all or whether one can only talk about disturbed functions will not be dealt with here. Nevertheless, all of the concepts under discussion assume that the symptoms of individual persons are generalised, classified, and traced back to common causes; see: Alvan R. Feinstein, *Clinical Judgement* (Baltimore: Williams & Wilkins, 1967); Banks, "From Dogs' Testicles to Mares' Urine: The Origins and Contemporary Use of Hormonal Therapy for the Menopause"; Kay Codell Carter, *The Rise of Causal Concepts of Disease: Case Histories*, History of Medicine in Context (Aldershot: Ashgate, 2003); Jon Arrizabalaga, "Problematising Retrospective Diagnosis in the History of Disease," *Asclepio* 54 (2002): 51–70; Graham W. Bradley, *Disease, Diagnosis and Decisions* (Chichester: Wiley & Sons, 1993); Alex Broadbent, "Causation and Models of Disease in Epidemiology," *Studies in History and Philosophy of Biological and Biomedical Sciences* 40 (2009): 302–311.

⁷³ For further detail on the following, see: Schlich, "Changing Disease Identities."

⁷⁴ George Stodart Blackie, *Cretins and Cretinism: A Prize Thesis of the University of Edinburgh* (Edinburgh: Maclachlan & Stewart, 1855); John McClelland, "Observations on Goitre," *Transactions of the Medical and Physical Society of Calcutta* 7 (1834): 145–155; James Reid, "On the History and Cause of Bronchocele or Goitre," *The Edinburgh Medical and Surgical Journal* 46 (1836): 40–76; Hugh Norris, "Notice of a Remarkable Disease, Analogous to Cretinism, Existing in the West of England," *The Medical Times* 17 (1847): 257–258; Joseph Adams, "On Goitre and Cretinism," *The Medical and Physical Journal* 33, no. 6 (1815): 433–447; David Lawson, "On the Prognosis of Cretinism," *Archives of Diseases in Childhood* 30 (1855): 75–82; Kinder Wood, "Observations Upon the Local Prevalence of Idiotism, and Its Connection with Goitre," *The Edinburgh Journal of Medical Science* 2 (1826): 194–198. This is not to imply the priority of those authors. For historical surveys see: Sigmund Bornhauser, *Zur Geschichte der Schilddrüsen- und Kropfforschung im 19. Jahrhundert unter besonderer Berücksichtigung der Schweiz* (Aarau: H.R. Sauerländer, 1951).

1883.⁷⁵ Most of the authors of these articles either practiced as doctors in areas where cases of cretinism were common, or went on extensive research trips to those places.⁷⁶ They firstly began by collecting data in a manner similar to contemporary natural historians and explorers, that is they began to investigate the phenomenon of cretinism in the areas where it occurred. They looked at ‘cretins,’ spoke with the local population, took notes, published their findings, and entered a heated discourse facilitated by professional medical journals. With their decidedly empirical approach, these authors were archetypical proponents of the widespread turn toward empirical evidence in scientific and medical discourses, a change that succeeded the interest in theory that had prevailed during the preceding era of what has been coined “romantic natural philosophy.”⁷⁷ While emphasising the inherent novelty of their own approach, however, the burgeoning empiricists often used the concepts of “natural philosophically”-orientated doctors as the basis for their own views. They also adopted the disease entity of cretinism from their predecessors as well as the idea that cretinism itself was a medical problem in the first place.⁷⁸ Like the followers of Johann Lukas Schönlein’s “natural history” school, those authors tried to determine a disease entity that allowed for a rational connection between the disease’s aetiology, its general course, its pathophysiological mechanisms, the reported and observed symptoms, and the therapeutic approaches to be used.⁷⁹ In order to arrive at such a general definition, they investigated diseases empirically,

⁷⁵ Ord et al., *Report of a Committee*. Although sporadic reference to the ideas presented in this report will be made throughout this chapter, its historical analysis will be part of chapter 2.

⁷⁶ Hugh Norris was a local practitioner in Chiselborough, Somerset, and described his findings of cretinism out of curiosity. Kinder Wood practiced in Derbyshire, where both goitre and cretinism appeared with frequency. John McClelland and George Blackie were part of the medical community of Edinburgh. Their involvement with cretinism and goitre was politically motivated, as will be discussed later.

⁷⁷ On “romantic” medicine see: Iago Galdstone, “The Romantic Period in Medicine,” *Bulletin of the New York Academy of Medicine* 35, no. 5 (1956): 346–362; George C Grinnell, “The Physiology of Romantic Medicine,” *Studies in Romanticism* 45, no. 2 (2006): 223–250.

⁷⁸ These authors dealt at some length with the concepts of their predecessors. For a summary of this aspect, see: Bornhauser, *Zur Geschichte der Schilddrüsen- und Kropfforschung im 19. Jahrhundert (unter besonderer Berücksichtigung der Schweiz)*, 7–39.

⁷⁹ The “natural history school” of medicine in the first half of the nineteenth century should not be confused with the natural history of the previous century. For Schönlein’s “natural historical” method,

like their colleagues in the field of natural history would investigate plants or animals in nature. Even though their models included autopsy to some extent, they attached no particular importance to either pathological anatomy or physiology for the purpose of clarifying the causes of this disease.⁸⁰ According to the travelling physicians Lawson and Adams, the “products” of disease, as represented by anatomical changes or an imbalance of fluids within the body, should not be regarded as its causes. Causal explanations had to be sought outside the patient afflicted by cretinism.⁸¹ They thus focused on one level of the whole hierarchy of causes that medicine would traditionally deal with. These causes differed from one another depending on their location inside or outside of the body and on their proximity to the phenomenon, i.e. whether they were a predisposition, direct, a trigger, etc.⁸²

As mentioned before, these doctors conducted their studies using the same or very similar techniques as comparative analyses of botanical and zoological specimens; they compared their respective clinical cases with the aim of establishing disease entities that corresponded to “nature.”⁸³ Part of this approach consisted of determining the typical—so-called pathognomonic—signs of individual diseases and differentiating them from other symptoms that also happened to be present in the same patient. This had to be done, according to George Blackie, without preconceptions, without having a prototype of cretinism as a disease in mind to begin with.⁸⁴

see: Johanna Bleker, *Die Naturhistorische Schule*, Medizin in Geschichte und Kultur (Stuttgart: Fischer, 1981), 43–80.

⁸⁰ Norris, “Notice of a Remarkable Disease, Analogous to Cretinism, Existing in the West of England”; Reid, “On the History and Cause of Bronchocele or Goitre”; McClelland, “Observations on Goitre”; Blackie, *Cretins and Cretinism: A Prize Thesis of the University of Edinburgh*.

⁸¹ Lawson, “Prognosis of Cretinism”; Adams, “On Goitre and Cretinism”; McClelland, “Observations on Goitre,” 143, 150.

⁸² On the different causal stages, see e.g. Lester S King, *Medical Thinking: A Historical Preface* (Princeton, N.J.: Princeton University Press, 1982), Chapter 9; José Peset and Gracia Diego, *The Ethics of Diagnosis*, vol. 40 (Kluwer, 1992); Carter, *The Rise of Causal Concepts of Disease: Case Histories*, Chapter 4.

⁸³ On the notion of the analogy between disease, entities and zoological and botanical species in the “natural history school”, see: Bleker, *Die Naturhistorische Schule*, 53–57.

⁸⁴ Blackie, *Cretins and Cretinism: A Prize Thesis of the University of Edinburgh*, 4–5.

As a result, the disease entity the authors described was much broader than what we today would identify as cretinism. For instance, different kinds of mental deficiency, goitre, dwarfism, albinism, and various ophthalmological disorders, and certain kinds of deafness were included undifferentiated.⁸⁵ Especially in comparison to our contemporary organ-centred concept, these authors conflated a variety of diseases in their proposed category of cretinism, among them a good many cases that by today's physicians' standards would probably be diagnosed as Down syndrome or epilepsy.⁸⁶

The perceived breadth of the disease entity was a direct consequence of the empirical approach: only registering the disease in all its forms would allow doctors to fit cretinism into a *natural* classification. They rejected the artificial systems of the eighteenth century, which, in their view, had been based on arbitrarily chosen symptoms. Deciding on the characteristic symptoms of the disease should only occur on the basis of all registered data.⁸⁷ Their extensive case histories therefore included long and detailed lists of possible symptoms.⁸⁸ Besides the physical particularities of the afflicted individuals, for instance, they also listed their idiosyncratic behaviour as well as clothes worn.

The difficulty consisted in deciding which cases were to be counted as cretinism, and which were to be excluded. Key symptoms could not be used, as these came by definition at the end of the investigations. In practice, most authors therefore proceeded in a different way: they

⁸⁵ Ibid., 4–6; McClelland, "Observations on Goitre," 148–149; Adams, "On Goitre and Cretinism," 439–440; Reid, "On the History and Cause of Bronchocele or Goitre," 50–55. This kind of breadth for a disease entity is typical for the period; see: Heinrich Mauri, *Die Entwicklung des Kretinenproblems: Die Kretinismusforschung im 19. Jahrhundert* (Freiburg: University of Freiburg, 1976), 74–84; Bornhauser, *Zur Geschichte der Schilddrüsen- und Kropfforschung im 19. Jahrhundert (unter besonderer Berücksichtigung der Schweiz)*, 76.

⁸⁶ Retrospective diagnosis is always problematic. But on this point, see: Schlich, "Changing Disease Identities," 433; Clark T. Sawin, "Goitre," in *The Cambridge World History of Human Disease* (Cambridge: Cambridge University Press, 1993), 750–756; Schlich and Tröhler, *The Risks of Medical Innovation*.

⁸⁷ Blackie, *Cretins and Cretinism: A Prize Thesis of the University of Edinburgh*, 98–101; Norris, "Notice of a Remarkable Disease, Analogous to Cretinism, Existing in the West of England," 257.

⁸⁸ Blackie, *Cretins and Cretinism: A Prize Thesis of the University of Edinburgh*, 194–195.

began their investigations from the premise that the land itself, the territory, formed its inhabitants, determined their constitution and thus consequently also their diseases. Hence, the locale where a disease occurred could be used as the decisive criterion for an attempt at identifying its underlying nature.⁸⁹

Consequently, Blackie counted cases of albinism, deafness, and mental deficiency as cretinism if they occurred in the endemic areas.⁹⁰ Cases that looked like cretinism but occurred outside these locales were discounted as being “rooted in a very different soil.”⁹¹ Thus, contrary to their underlying research programme, these authors were using geography as the basis for their respective diagnoses and not the clinical picture.⁹² Their reliance on geography is apparent in the medical dictionary definition of the disease, which was distilled out of these reports by 1855. According to these reports cretinism is a “chronic, congenital or acquired disease of the whole body, caused by endemic influences, occurring only in the Alpine mountain ranges, distinctive in nature, featuring a lack of common sense, a lack of articulate human speech and a characteristic expression of imbecility or brutality on the face of the person suffering from it.”⁹³

1.3. THE METHODOLOGICAL PROBLEM OF CAUSAL ATTRIBUTION

Some of these authors combined their empirical and observational research method with a rather particular procedure for the investigation of disease. This approach is especially interesting for the argument of this thesis, because the reconfiguration of thyroid dysfunction

⁸⁹ Reid, “On the History and Cause of Bronchocele or Goitre,” 42–45; Blackie, *Cretins and Cretinism: A Prize Thesis of the University of Edinburgh*, 138. The dilemma described is typical for this period. The diagnosis of cretinism in individual cases repeatedly confronted investigators with major problems at the time, see: Mauri, *Die Entwicklung des Kretinenproblems: Die Kretinismusforschung im 19. Jahrhundert*, 80; Schlich, “Changing Disease Identities,” 437.

⁹⁰ Blackie, *Cretins and Cretinism: A Prize Thesis of the University of Edinburgh*, 132, 134.

⁹¹ *Ibid.*, 202.

⁹² Adams, “On Goitre and Cretinism,” 439.

⁹³ Blackie, *Cretins and Cretinism: A Prize Thesis of the University of Edinburgh*, 199.

and the development of organ replacement therapy went along with a characteristic transformation of ideas about the causation of disease. In the course of this specific transformation, medical doctors and scientists started to focus primarily on what they called *necessary causes*—that is, on the causes without which a disease does not and cannot occur. As the example of bacteriology illustrates, it were these necessary causes that medical science was beginning to investigate in the course of the second half of the nineteenth century.⁹⁴ This change in perception was also of central importance for the development of organ replacement therapy.

Rather than investigating necessary causes, the vast majority of the cases published were assembling large numbers of seemingly unrelated causes of cretinism. However, what connected them all was the so-called *endemic constitution*, which is understood as the overall sum of the characteristic features of the locale where a certain disease occurs.⁹⁵ These authors presented the endemic constitution as that particular factor without which cretinism did not occur. To the modern reader, at first glance this factor appears to be a necessary cause of cretinism. Closer inspection, however, reveals at least two major problems with this kind of explanation. The first can be characterised as a methodological reservation. According to the prevailing research approach, these authors claimed to determine the cause of cretinism on the basis of empirical and observational data. In actuality, however, they had already introduced the cause of cretinism, which was still supposed to be determined, into their research during the initial phase of collecting the data, namely when they had to decide whether a person displaying the symptoms counted as a cretin or not. Philosophically

⁹⁴ For a discussion of this change see: Carter, *The Rise of Causal Concepts of Disease: Case Histories*; Kay Codell Carter, "The Development of Pasteur's Concept of Disease Causation and the Emergence of Specific Causes in Nineteenth-Century Medicine," *Bulletin of the History of Medicine* 65 (1991): 528–529.

⁹⁵ Schlich, "Changing Disease Identities," 233.

speaking, this is obviously a case of circular logic: the choice of a certain definition of disease already determined what they would later find to be the cause of the disease itself.⁹⁶

The second problem becomes evident when we try to reconstruct the concrete conditions constituting the described endemic constitution. When examined closely, the endemic constitution turns out to contain numerous partial causes, none of which is singularly necessary when we begin to consider them individually. This complication is evident in most works written about cretinism. In Blackie's work, for example, it depended on certain properties of the terrain: the altitude, the geographical longitude as well as latitude, the topographical shape of the landscape, and the like.⁹⁷ Cretinism was usually found in secluded places, in the close curvature of valleys, in basins with narrow outlets. The presence of water seemed to be typical as well, because cretinism often occurred in areas where the ground was permanently damp and swampy.⁹⁸ In addition, high humidity and frequent and sudden changes in the environmental temperature appeared to be highly common. What is described here is only a relative causal necessity. More specifically, only part of the conditions listed were known to produce cretinism in some of the cases. In addition, many of the factors described need not be present in fully developed form, their effect rather being dependent on how they combined with each other and with various non-endemic partial causes. The larger the number of causative factors, the higher the incidence rate of cretinism and *vice versa*. In the extreme case, as we will find out in the next chapter, the 'necessary' cause does not appear at all. Non-endemic causes alone produce cretinism in this case—in other words, the causes that these authors listed were ultimately not necessary at all.

Nor were these causes really sufficient. Based on their combined wealth of experience, authors like Blackie knew or had heard of regions where all the enumerated conditions were

⁹⁶ See: Carter, *The Rise of Causal Concepts of Disease: Case Histories*, 98–110.

⁹⁷ Blackie, *Cretins and Cretinism: A Prize Thesis of the University of Edinburgh*, 178–179.

⁹⁸ *Ibid.*, 179.

present without even a single case of cretinism being reported or observed. Thus, additional partial causes had to be brought into the picture to create the disease. These causes included poverty, a stark lack of education, poor and insufficient accommodation, inadequate clothing and nutrition; in some cases even reduced atmospheric electricity, and so on. Their journals accumulated factor after factor without the ability to exclude any of them as irrelevant to the development of cretinism.

What at first glance then seemed like a necessary cause for cretinism thus turned out to be a factor that was neither necessary nor sufficient. The difficulties in grasping the cause of the disease became even more obvious in the works of Norris, Reid and McClelland.⁹⁹ Unlike Blackie, they did not regard any single necessary factor as the cause of cretinism.¹⁰⁰ Instead, they compiled extensive lists of causes and, in the end, actually enumerated all of the special features they had observed in the endemic areas, without being able either to evaluate their relative importance or to eliminate any of them as insignificant.¹⁰¹ These lists came to include all the differences between the hilly regions and the plains and registered characteristic natural features such as flora, fauna, and climate. It portrayed the population in terms of their nutrition, clothing, accommodation, and work, but it did not determine any one of these factors as necessary.¹⁰² Which detail was important in each individual case could never be known in advance.¹⁰³

⁹⁹ Norris, "Notice of a Remarkable Disease, Analogous to Cretinism, Existing in the West of England," 258; McClelland, "Observations on Goitre," 154; Reid, "On the History and Cause of Bronchocele or Goitre," 59–63.

¹⁰⁰ Reid, "On the History and Cause of Bronchocele or Goitre," 70–71; McClelland, "Observations on Goitre," 155.

¹⁰¹ Reid, "On the History and Cause of Bronchocele or Goitre," 75.

¹⁰² Ibid., 73.

¹⁰³ McClelland, "Observations on Goitre," 150.

The compilers of these kinds of accounts collected a huge amount of data. They followed the empirical tradition of medical topography¹⁰⁴ and came up with extremely detailed descriptions of the endemic locales. They described special geographical features, geology, vegetation, agriculture, population density and dissemination, climate, quality of drinking water, buildings, and housing. And in regard to the inhabitants of the affected areas, they recorded their descent, profession, social conditions, nutrition, hygienic states, morals, customs, religion, and physical and mental constitutions, as well as the general frequency of illnesses.¹⁰⁵

On the basis of this data, Blackie came to the conclusion that only the whole, the “bundling together of all the endemic influences of a certain area,” could be regarded as “the one essential, obligatory, ultimately *necessary* cause producing cretinism,” and that these endemic influences were “almost innumerable.” He stated that it was a “sheer impossibility to recognise and list all the endemic influences and possible combinations thereof,” and that it was therefore also an “impossibility to enumerate and describe individually the causes that produce this condition, to prove the origin and the affliction with certainty—and to investigate the share that individual influences have in its onset and outbreak.”¹⁰⁶

These findings, of course, had consequences for the way that the disease was handled. Even though it was the authors’ declared goal to increase the store of knowledge for the prevention and therapy of cretinism, the issue of therapy was implicitly sidelined.¹⁰⁷ For most

¹⁰⁴ For this genre and its connections to medical science and public health, see: Jan Brügelmann, *Der Blick Des Arztes Auf Die Krankheit Im Alltag 1779-1850* (Berlin: Freie Universität Berlin, 1982), 161–179.

¹⁰⁵ Reid, “On the History and Cause of Bronchocele or Goitre”; Norris, “Notice of a Remarkable Disease, Analogous to Cretinism, Existing in the West of England”; McClelland, “Observations on Goitre”; Blackie, *Cretins and Cretinism: A Prize Thesis of the University of Edinburgh*; William Robinson, *Endemic Goitre or Thyreoele* (London: Churchill, 1883).

¹⁰⁶ Blackie, *Cretins and Cretinism: A Prize Thesis of the University of Edinburgh*, 161–163. Emphasis added.

¹⁰⁷ *Ibid.*, 8.

of them, combatting the disease lay well beyond the scope of their publications and none devoted more than a page to this issue.¹⁰⁸

Some prophylactic measures, however, were proposed. The most radical advised leaving the endemic areas.¹⁰⁹ These proposals impacted a whole range of partial causes and required public measures to redevelop areas affected by cretinism: draining the soil, diverting rivers, keeping the villages clean, building new and better roads to further the optimisation of the infrastructure. It was suggested that detailed and standardised building regulations were needed to make sure that houses were set up properly only in elevated locations and as far as possible from any bodies of water present in the area. It was also emphasised that large parts of the population could not afford adequate nutrition and that farmers did not own enough land to support themselves by farming. In order to prevent cretinism, the state was to intervene and regulate these matters.¹¹⁰ This aspect of cretinism therefore had an additional political dimension. This kind of public engagement was characteristic for the adherents of empirical medicine in the mid-nineteenth century. Doctors at the time often showed a great amount of sensitivity to social problems and frequently became involved in politics.¹¹¹ Blackie, for instance, demanded reforms that were sweeping, expensive, and decidedly political. He was a philanthropist and member of a temperance society in Edinburgh (which might explain his call for the restriction in alcohol consumption).¹¹²

¹⁰⁸ Reid, "On the History and Cause of Bronchocele or Goitre," 61; McClelland, "Observations on Goitre," 151–152; Blackie, *Cretins and Cretinism: A Prize Thesis of the University of Edinburgh*, 78–80.

¹⁰⁹ Blackie, *Cretins and Cretinism: A Prize Thesis of the University of Edinburgh*, 80.

¹¹⁰ *Ibid.*, 202–207.

¹¹¹ See: Schlich, "Changing Disease Identities," 439–440. On the perception of social ills by the authors of medical topographies, see: Brügelmann, *Der Blick Des Arztes Auf Die Krankheit Im Alltag 1779-1850*, 158–159. Specifically on cretinism in this connection, see: Mauri, *Die Entwicklung des Kretinenproblems: Die Kretinismusforschung im 19. Jahrhundert*, 45–51; Adams, "On Goitre and Cretinism," 440–441; Lawson, "Prognosis of Cretinism," 79.

¹¹² In his demands, Blackie included a complete list of proposals that the Edinburgh Temperance Society had submitted to the Queen; Blackie, *Cretins and Cretinism: A Prize Thesis of the University of Edinburgh*, 239.

On top of his proposed measures for preventing cretinism, Blackie advocated a therapeutic programme for curing those individuals who were already affected by it. Contrary to prevailing opinion – in Britain and on the Continent – Blackie believed in the curability of the ailment.¹¹³ For evidence, he referred to the positive reports coming from Johann Jakob Guggenbühl's mountain-top sanatorium for cretins on the Abendberg near Interlaken, in Switzerland. Abendberg was the model for a veritable surge of similar establishments. Guggenbühl claimed to have cured cretins by taking them out of their environments and thus the harmful influences exhibited there. The change of environment was complemented by a range of measures to eliminate the additional triggers of cretinism. These measures included mental and physical training as well as emotional support and pharmaceutical, surgical, or other treatments.¹¹⁴

Environmental concerns affected Blackie and other doctors' medical view of cretinism. Their strategy for dealing with the problem of cretinism, however, was very different from the way later doctors tried to solve the issue; and it was a strategy that ultimately failed. Instead of concentrating on a central pattern of causes, these early researchers accumulated disconnected facts without being able to determine their importance. As it was never certain which cause would be operative in a particular case, the battle had to be fought on all fronts at the same time. Still, outbreaks of the disease could not be prevented. If a disease occurred despite all precautionary measures taken, a new factor had to be added to the list of causes.¹¹⁵ In their analysis, Blackie and others were unable to convince the authorities that it

¹¹³ Ibid., 198–212.

¹¹⁴ Leo Kanner, "Johann Jakob Guggenbühl and the Abendberg," *Bulletin of the History of Medicine* 33 (1959): 494. On this concept and other similar undertakings at the time, see: Mauri, *Die Entwicklung des Kretinenproblems: Die Kretinismusforschung im 19. Jahrhundert*, 106–107. For the British context, see: Robinson, *Endemic Goitre or Thyreocoele*, 205–207.

¹¹⁵ See: Latour, *The Pasteurization of France*, 19–22.

was worth implementing any multifarious and sweeping but ultimately uncertain preventative measures.¹¹⁶

Things did not turn out any better for therapy at the individual level, either. In Switzerland, Guggenbühl's concept failed spectacularly. After a short period of enthusiasm, accompanied by an outpouring of donations, endowments, as well as fame and glory for Guggenbühl himself, the tides turned. It appeared that the approach was not able to live up to what it had promised.¹¹⁷ In 1838, the authorities had the facility on the Abendberg closed and turned it into a psychiatric institute for children.¹¹⁸

It took decades for a more powerful and useful concept for understanding and treating cretinism to be developed. Subsequent surveys of the subject kept referring to these earlier examples as models. With only very few variations, cretinism surveys included the same breadth of the disease entity, the same large number of non-necessary causes of the disease, and the same significance of locale for the genesis of the condition. The same uncertainty pertained to theory and treatment of cretinism.¹¹⁹ In 1883—the same year that Theodor Kocher introduced a completely new approach to cretinism, an approach I will discuss in the next section—one author still claimed that “the farther research progresses, the more the places of observation the investigations spread to, the greater the differences that emerged in the view of individual observers, the more varied theories accumulated, and today after

¹¹⁶ See: Mauri, *Die Entwicklung des Kretinenproblems: Die Kretinismusforschung im 19. Jahrhundert*, 113–118. See also the difficulties of the French hygienists in: Latour, *The Pasteurization of France*, 20–21, 33.

¹¹⁷ Kanner, “Johann Jakob Guggenbühl and the Abendberg,” 496–500.

¹¹⁸ W. Rushton Parker et al., “A Discussion on Sporadic Cretinism in This Country and Its Treatment,” *British Medical Journal* 2 (1896): 634. For the Swiss context see: Mauri, *Die Entwicklung des Kretinenproblems: Die Kretinismusforschung im 19. Jahrhundert*, 99–103.

¹¹⁹ Bornhauser, *Zur Geschichte der Schilddrüsen- und Kropfforschung im 19. Jahrhundert (unter besonderer Berücksichtigung der Schweiz)*, 34–43; Mauri, *Die Entwicklung des Kretinenproblems: Die Kretinismusforschung im 19. Jahrhundert*, 11–54; Schlich, “Changing Disease Identities,” 433; Ulrich Tröhler, “Die Wechselwirkung von Anatomie, Physiologie und Chirurgie im Werk Theodor Kochers und einiger Zeitgenossen,” in *Theodor Kocher 1841-1917*, ed. Urs Boschung (Bern: Hans Huber, 1991), 55.

unbiased examination one must admit that the cause *of the endemics of goitre and cretinism* is still in the dark.”¹²⁰

By the 1870s, the concept of cretinism remained environmentally based, and was still rooted in an approach that favoured the symptomatic description over causal attribution. Although the characterisation of cretinism in Britain took on a decidedly political dimension. Without viable treatment or even prophylactic options, the environmental therapy of Blackie remained impractical and unpersuasive. In Berne, Switzerland, however, the surgeon Theodor Kocher was about to develop an organ-based concept of goitre and cretinism that helped to redefine those conditions as thyroid insufficiency diseases.

1.4. GOITRE AND THE INVENTION OF THE SURGICAL THYROID REPLACEMENT THERAPY

The first surgical organ replacement in 1883 was undertaken to reverse the undesirable consequences of a previous extirpation. Theodor Kocher had introduced the practice of removing the whole thyroid gland—instead of the usual process of reducing the organ’s size by partial excision—in order to prevent the recurrence of goitre. Kocher had so perfected his surgical technique that he was able to remove the whole gland in a series of patients without fatal results. He did not notice the consequences of his total thyroidectomies until later.

Goitre posed a serious medical problem. Before Kocher’s time, it was not uncommon for doctors to be forced to stand by and watch a patient be asphyxiated by his goitre. A surgical solution to the problem of goitre only became conceivable and viable once antisepsis, anaesthesia, and improved surgical techniques had helped surgery to extend its domain to more and more regions of the body. At first, most of this new surgery was concerned with what became known as resection: based on a localistic understanding of disease, surgeons

¹²⁰ Robinson, *Endemic Goitre or Thyreocoele*, 123.

would remove pathological tissue, such as cancerous growths, inflammations, and abscesses.¹²¹ Goitre was among the diseases that were localised and could therefore be removed surgically. A goitre operation, which until Kocher meant partial excision, was one of the several resections performed prior to his new surgical technique, but the most common was amputation.¹²² However, surgeons had long refused to conduct thyroidectomies, partial or not. Their inability to handle the technical difficulties, and the patients' blood loss, had resulted in a prohibitively high mortality rate.¹²³ Only in the late 1870s did the operation become more common—a development that Kocher saw as “excellent proof of the rise of operative surgery.”¹²⁴ It was mainly Kocher himself, who developed the surgical techniques necessary to master this practical intervention.¹²⁵ The actual function of the thyroid gland as an organ remained in the dark, however, and doctors and medical scientists could do no more than guess at its purpose. Even leading physiologists such as Claude Bernard had no clue.¹²⁶ Surgeons, therefore, tacitly assumed that the thyroid had no function at all, as both Kocher and the English experimental physiologist Victor Horsley wrote retrospectively.¹²⁷ Thus, without a special reason to investigate this topic more closely, and in view of the impression

¹²¹ Ulrich Tröhler, “Surgery (Modern),” in *Companion Encyclopaedia of the History of Medicine*, ed. William F Bynum and Roy Porter, vol. 2 (London: Routledge, 1993), 987.

¹²² Paul Sick, “Über die totale Exstirpation einer kropfig entarteten Schilddrüse und über die Rückwirkung dieser Operation auf die Circulationsverhältnisse am Kopfe,” *Medizinisches Korrespondenzblatt des Württembergischen ärztlichen Vereins* 37 (1867): 199; Theodor Kocher, “Die Indicationen zur Kropfexstirpation beim gegenwärtigen Stande der Antisepsis,” *Korrespondenzblatt für Schweizer Ärzte* 9 (1892): 226.

¹²³ Schlich suggests that before 1880 the overall mortality rate in Germany and Switzerland alone, resulting from partial thyroidectomies was in the region of 86%; see Schlich, “Changing Disease Identities,” 433.

¹²⁴ Kocher, “Die Indicationen zur Kropfexstirpation beim gegenwärtigen Stande der Antisepsis,” 226. For goitre surgery see also: Bornhauser, *Zur Geschichte der Schilddrüsen- und Kropfforschung im 19. Jahrhundert (unter besonderer Berücksichtigung der Schweiz)*, 44–53; Ulrich Tröhler, *Der Nobelpreisträger Theodor Kocher 1841-1917: Auf dem Weg zur Physiologischen Chirurgie* (Basel: Birkhäuser, 1984), 121–126.

¹²⁵ Tröhler, *Theodor Kocher*, 121–123.

¹²⁶ *Ibid.*, 124.

¹²⁷ Victor Alexander Hayden Horsley, “Thyroid” (London, 1896), Wellcome Manuscript Collection; MS 6029/2; Victor Alexander Hayden Horsley, “Some Researches Carried Out During the Last Ten Years into the Functions of the Brain and the Thyroid Gland” (London, 1899), Wellcome Manuscript Collection; Theodor E. Kocher, “Über Kropfextirpation und ihre Folgen,” *Archiv für Klinische Chirurgie* 29 (1883): 254.

that there were “no accolades to be earned in the field of vascular organs, particularly the thyroid,”¹²⁸ as an observer remarked in 1886, the organ attracted very little attention at all. The dangers posed by an untreated goitre, however, were obvious, and even surgically treated goitres had a well-known tendency to grow back from gland tissue that had not been removed in the operation. From a surgical point of view, the logical step was therefore to remove the afflicted organ in its entirety. In 1882, Kocher reported a total of 125 extirpations in the literature to date, with a mortality rate of only 14.1 per cent.¹²⁹ Even though the first indications of the harmfulness of total thyroid removals had appeared even before that date, doctors tended to pay little attention to it.¹³⁰ Surgeons were mostly concerned with the mortality rate associated with the operation itself. A case was considered completed successfully once the wound had healed satisfactorily.¹³¹

On September 7, 1882, at the International Congress of Hygiene in Geneva, Switzerland, Kocher met the local surgeon Jacques-Louis Reverdin (1842–1929).¹³² A year earlier, Reverdin had noticed that two adult patients had developed a specific set of symptoms, apparently as a side effect of the total thyroidectomy they had undergone. One patient’s appearance reminded him strongly of cretinism. Asked about similar cases, Kocher recalled having seen a similar phenomenon a few years back. Reverdin presented his observations a week later, on September 13, at the annual meeting of the Geneva Medical Society. He advised his

¹²⁸ Charles Turrington, “The Extirpation of the Thyroid Gland: An Experimental Study,” *Archive for Experimental Pathology* 21 (1886): 397.

¹²⁹ Kocher, “Die Indicationen zur Kropfextirpation beim gegenwärtigen Stande der Antisepsis,” 267; Sick, “Über die totale Exstirpation einer kropfig entarteten Schilddrüse und über die Rückwirkung dieser Operation auf die Circulationsverhältnisse am Kopfe.” For Kocher’s quantifications see: Tröhler, *Theodor Kocher*, 97–120.

¹³⁰ Sick, “Über die totale Exstirpation einer kropfig entarteten Schilddrüse und über die Rückwirkung dieser Operation auf die Circulationsverhältnisse am Kopfe,” 204; Kocher, “Über Kropfextirpation und ihre Folgen,” 20; Tröhler, *Theodor Kocher*, 125.

¹³¹ Tröhler, *Theodor Kocher*, 125.

¹³² This and the following are based on *Ibid.*, 126–130. See also: Kocher, “Über Kropfextirpation und ihre Folgen,” 20–30.

colleagues against performing total thyroidectomies and decided always to leave a part of the thyroid gland tissue behind when performing his own goitre operations.¹³³

Kocher, for his part largely unaware of this phenomenon beyond his brief anecdotal recollection of the above mentioned occurrence, started to conduct extensive follow-up examinations.¹³⁴ The findings dealt a heavy blow to his theories about complete thyroidectomy: while the patients who had received a partial thyroidectomy seemed largely to enjoy excellent health, those who had undergone a total extirpation of the thyroid gland were almost unrecognisable. They complained about fatigue, weakness, heavy and cold limbs, reduced mental abilities and alertness, swollen hands and feet, hair loss, and anaemia. Furthermore, their bloated faces gave them the appearance of “idiots.”¹³⁵ The worst of those affected were the younger patients who had undergone the operation whilst they were still growing: their growth had been retarded and they displayed the appearance of cretins.¹³⁶ Notably enough, the only two patients who were not displaying these disconcerting signs had suffered a relapse of their goitre, which had grown from a piece of the thyroid left behind during the operation. To Kocher, “the connection to idiotism and cretinism was now unmistakable.”¹³⁷ As a name for the affliction he proposed *cachexia strumipriva*, which indicated that the disorder resulted from goitre removal without making any commitment to the exact reason why.¹³⁸ Kocher’s theory on the disease mechanism still remained completely within the localistic framework. He maintained the view that the thyroid regulated the blood

¹³³ “Société Médicale de Genève, Séance du 13 Septembre 1882.” No transcript survived, but for a discussion see Tröhler, *Theodor Kocher*, Chapter 3.

¹³⁴ Kocher, “Über Kropfextirpation und ihre Folgen,” 20–32; Bornhauser, *Zur Geschichte der Schilddrüsen- und Kropfforschung im 19. Jahrhundert (unter besonderer Berücksichtigung der Schweiz)*, 53–64; Tröhler, *Theodor Kocher*, 127–128.

¹³⁵ Tröhler, “Die Wechselwirkung von Anatomie, Physiologie und Chirurgie im Werk Theodor Kochers und einiger Zeitgenossen,” 64.

¹³⁶ Schlich, “Changing Disease Identities,” 433.

¹³⁷ Kocher, “Über Kropfextirpation und ihre Folgen,” 31.

¹³⁸ *Ibid.*, 32. *Cachexia strumipriva* designates physical weakness caused by the removal of goitre.

circulation in the region of the neck and head and ascribed the observed symptoms to a failure of this function.¹³⁹

Kocher communicated his observations and conclusions in a lecture at the twelfth congress of the German Surgical Society on April 4, 1883. The audience's reaction was divided. A great many of his colleagues thought that cretinism and goitre represented but different stages of the same endemically caused illness. Kocher's patients, they argued, had just gone from one stage to the next, regardless of the operation. The occurrence of cretinism after a goitre removal operation had, after all, been observed in geographical regions where both afflictions often appeared in combination.¹⁴⁰

In June of the same year, a substantial article by Reverdin gave a detailed account of twenty-two cases of total thyroid extirpation. He first described troubles appearing right after the operation, including the pronounced tendency to convulsions and the appearance of tetany, which were differentiated from the long-term impact of the intervention. As possible disease mechanisms behind these pathological phenomena Reverdin discussed the lack of a specific function of the thyroid and the damage incurred by the nervous system during the surgery itself.¹⁴¹ Because side effects of the operation only appeared after the total extirpation of the thyroid gland, however, he ascribed a crucial role to the absence of the organ. He called for fundamental experimental research to be conducted in order to elucidate the function of the

¹³⁹ Ibid., 32–47; Tröhler, *Theodor Kocher*, 128–130.

¹⁴⁰ V. Bardeleben, "Diskussionsbeitrag zu Kocher's 'Über die Kropfextirpation und ihre Folgen'," *Verhandlungen der Deutschen Gesellschaft fuer Chirurgie* 12, no. 2 (1883): 4–9. See also Kocher's comments on the subject in retrospect: Theodor Kocher, "Die Schilddrüsenfunktion im Lichte neuer Behandlungsmethoden verschiedener Kropfformen," *Correspondenzblatt für Schweizer Ärzte* 25 (1895): 10. For the contradictory and little-regarded physiological experiments with thyroidectomy before 1883, performed by Bardeleben (1841) and others, see: Bornhauser, *Zur Geschichte der Schilddrüsen- und Kropfforschung im 19. Jahrhundert (unter besonderer Berücksichtigung der Schweiz)*, 39–42.

¹⁴¹ This hypothesis was also taken over by others, e.g. A Mayor, "La Cachexie Pachydermique," *Revue Médicale de La Suisse Romande* 3 (1883): 532–539. Bornhauser, *Zur Geschichte der Schilddrüsen- und Kropfforschung im 19. Jahrhundert (unter besonderer Berücksichtigung der Schweiz)*, 115–121.

thyroid, and in order to explain the connection between cretinism and the post-thyroidectomy syndrome Kocher called *cachexia strumipriva*.¹⁴²

Even though these discussions are often interpreted as representing the discovery of thyroid function, the matter was actually by no means settled at this point. The hypothesis of a specific function of the thyroid and its role in certain pathological conditions was far from being generally accepted. As one commentator stated in 1886, “the state of the thyroid question today [is] no different than twenty years before.”¹⁴³ Furthermore, entirely unimpressed by Kocher’s warnings, many surgeons continued to perform total extirpations of the thyroid gland.¹⁴⁴ As another observer remarked in retrospect, it would “take a long time and a lot of work” to make the new concept prevail in the medical community.¹⁴⁵

Part of the process of establishing and defining the thyroid’s function involved experimental physiology. Some authors had already characterised the surgeons’ thyroidectomies as an unintentional physiological experiment—a *vivisection humaine*.¹⁴⁶ Subsequently, the subject was picked up by experimental physiologists, who investigated it with the help of animal experiments. The first was the German physiologist Moritz Schiff (1823–1896) during January 1884. He had already made similar observations on animals after thyroidectomies during 1856–1857, but had not pursued the matter further at that time.¹⁴⁷ Inspired by the new reports he now returned to his investigations. Among the short-term side effects of thyroidectomy, Schiff noted muscular twitches, trembling, and spasms up to the point of

¹⁴² Bornhauser, *Zur Geschichte der Schilddrüsen- und Kropfforschung im 19. Jahrhundert (unter besonderer Berücksichtigung der Schweiz)*, 64–71. The almost synchronous statements by Kocher and Reverdin later caused each of them to fiercely to dispute the other’s claim to priority in the discovery of thyroid function; see *Ibid.*, 74–113; Schlich and Tröhler, *The Risks of Medical Innovation*.

¹⁴³ Turrington, “The Extirpation of the Thyroid Gland: An Experimental Study,” 413.

¹⁴⁴ Ord et al., *Report of a Committee*, 21 (Supplement):94–137.

¹⁴⁵ On internal secretion see: Biedl, *The Internal Secretory Organs: Their Physiology and Pathology*, 10.

¹⁴⁶ Henry-Claude Lombard, “Sur Les Fonctions Du Corps Thyroïde D’après Des Documents Recents,” *Revue Médicale de La Suisse Romande* 3 (1883): 594.

¹⁴⁷ J. Moritz Schiff, “Bericht über eine Versuchsreihe betreffend der Wirkungen der Exstirpation der Schilddrüse,” *Archiv für Experimentelle Pathologie und Pharmakologie* 18 (1884): 25.

complete rigidity in his laboratory animals.¹⁴⁸ This was essentially the same phenomenon Reverdin had already described as a side effect of the goitre operation in humans and which was generally known as ‘tetany.’ Schiff believed that the thyroid contributed to the nourishment of the central nervous system, possibly by delivering a particular substance to the blood.¹⁴⁹ Organ removal, as used by Schiff, was to become the most important method for studying the function of other organs as well. Thyroid studies thus became paradigmatic for this kind of research.¹⁵⁰

After 1883, reports on the negative consequences of total thyroidectomy started to accumulate. They seemed to confirm that the organ had some vital function, even though evidence for the causal relationship between organ removal and symptoms was still lacking.¹⁵¹ Dissatisfaction with the ambiguity of the clinical observations caused many researchers to emulate Moritz Schiff and resort to the methods of experimental physiology. Thus, during the 1880s, medical scientists were busy conducting numerous experiments on the topic in almost all European countries.¹⁵² In 1891, Eugène Gley (1857–1930), professor of physiology at the Collège de France in Paris, referred to three hundred publications related to experimental trials of this kind.¹⁵³ The very fact that thyroid removal was regularly followed by a particular set of symptoms, and finally by the animal’s death, made the organ-centred disease concept increasingly convincing.¹⁵⁴

¹⁴⁸ Ibid., 34.

¹⁴⁹ Ibid.

¹⁵⁰ William F Bynum, “‘C’est Un Malade’: Animal Models and Concepts of Human Disease,” *Journal of the History of Medicine and Allied Sciences* 45 (1990): 404–411.

¹⁵¹ Turringdon, “The Extirpation of the Thyroid Gland: An Experimental Study,” 389.

¹⁵² Thomas Drobnick, “Experimentelle Untersuchungen über die Folgen der Exstirpation der Schilddrüse,” *Archiv für Experimentelle Pathologie und Pharmakologie* 25 (1889): 137.

¹⁵³ Eugène Gley, “Sur les fonctions du corps thyroïde,” *Comptes rendus de Société de Biologie* 48 (1891): 429–435.

¹⁵⁴ For experiments conducted in Glarus (1884), in Vienna, and in Canalis, see: Bornhauser, *Zur Geschichte der Schilddrüsen- und Kropfforschung im 19. Jahrhundert (unter besonderer Berücksichtigung der Schweiz)*, 129–131. For others, see: Turringdon, “The Extirpation of the Thyroid Gland: An Experimental Study.”

The methods of experimental physiology made it possible to examine and precisely differentiate the effects of various manipulations on the living organism. Charles Turringdon, surgeon to the Middlesex Hospital in London, for instance, used animals to imitate methodically all the damage caused by a normal goitre removal in order to pinpoint the causes of postoperative side effects.¹⁵⁵ He found that merely obliterating the blood vessels in the neck next to the organ did not lead to the typical postoperative symptoms, which was in direct contradiction to the theory that thyroidectomy disrupted the regulation of blood flow to the brain and thus brought on the symptoms. Turringdon's additional observation that not even the selective destruction of nerves resulted in the typical symptoms refuted the frequently advocated neural explanation of the phenomenon. This discovery held particular significance because it was especially tetany with its neurological character that had caused many researchers to identify nerve damage as the cause of any negative side effects after extirpation.¹⁵⁶

In order to be able to differentiate between the systemic effect of a lack of specific organ function and the effect of structural damage on the nerves and blood vessels in the region of the neck, experimenters changed the location of the organ by transplanting it in order to see whether or not the typical symptoms occurred. Schiff carried out this type of transplantation in order to verify his thesis about the existence of a non-localised chemical effect of the organ on the body. He grafted the thyroid of a dog into the abdominal cavity of a member of the same species. When he then removed the recipient animal's own thyroid, the side effects of the removal either did not appear at all or surfaced only in a very reduced form. Hence, according to Schiff, the thyroid evidently had a systemic function that it could exercise even outside its normal location. The side effects of its removal were therefore not attributable to

¹⁵⁵ Turringdon, "The Extirpation of the Thyroid Gland: An Experimental Study." For biographical information, see: Isidore Fischer, *Biographisches Lexikon der hervorragenden Ärzte der letzten Fünfzig Jahre*, Reprint (Munich: Urban & Schwarzenberg, 1962), vol. 2: 465.

¹⁵⁶ Turringdon, "The Extirpation of the Thyroid Gland: An Experimental Study," 399.

local damage to nerve centres, blood vessels, or the trachea, since these structures had remained unaffected by the presence or absence of thyroid tissue in the abdominal cavity.¹⁵⁷

The ability to provoke the changes that occurred after thyroidectomy—those that were equated with cretinism—and then to eliminate them again by removing and adding thyroid tissue independently of other factors was a very effective argument in helping the concept of organ replacement therapy to gain a foothold.¹⁵⁸ In fact, the procedure of isolating, removing, and replacing an organ in the living organism became an important method for investigating organ functions in general.¹⁵⁹ In terms of disease causation, this meant that the removal of the organ was the test that showed that the organ's absence sufficed to cause the disease. Kocher therefore ventured in 1884: "Experience gained and animal experiments performed so far have ... adequately proven that the total removal of the thyroid is the *sufficient cause* of cachexia."¹⁶⁰ In order to prove whether this cause was necessary as well—that is, that the phenomenon did not occur without the complete removal of the thyroid gland—reinsertion of the organ into the body had to be studied. If the implantation prevented the symptoms, then the absence of the organ was their necessary cause.

Organ replacement was thus a typical technique of experimental physiology whereby a phenomenon was only considered explained once the experimenter could provoke and arrest it at will.¹⁶¹ Physiologists aimed at controlling vital processes; it did not suffice merely to observe and describe them. Control could be achieved by determining necessary causes. It

¹⁵⁷ J. Moritz Schiff, "Resume d'une nouvelle serie d'experiences sur les effets de l'ablation des corps thyroïde," *Revue Médicale de la Suisse Romande* 4 (1884): 25–34.

¹⁵⁸ Schlich, *The Origins of Organ Transplantation: Surgery and Laboratory Science, 1880-1930*, 51.

¹⁵⁹ See, e.g.: Drobnick, "Experimentelle Untersuchungen über die Folgen der Exstirpation der Schilddrüse."

¹⁶⁰ Kocher, "Die Schilddrüsenfunktion im Lichte neuer Behandlungsmethoden verschiedener Kropfformen," 10. Emphasis in original.

¹⁶¹ Anne M Fagot-Largeault, "On Medicine's Scientificity: Did Medicine's Accession to Scientific 'Positivism' in the Course of the Nineteenth Century Require Giving up Causal (Etiological) Explanation?," in *Science, Technology, and the Art of Medicine: European-American Dialogues*, ed. Corinna Delkeskamp-Hayes and Mary Ann Gardell Cutter (Dordrecht: Kluwer, 1993), 111.

was exactly this task that Claude Bernard assigned to researchers in his *Introduction to Experimental Medicine* in 1865. They should identify the necessary conditions of life processes, he wrote, by increasing their power over them up to the point that they were able to make them appear and disappear arbitrarily.¹⁶²

The collected facts at least made it possible to abandon the theory of environmental causation of goitre, cretinism, and *cachexia strumipriva*—the endemic cause as proposed earlier and discussed at the beginning of this chapter. Even at the time of the developments outlined above, this traditional notion about the cause of disease was still widespread, and until the early 1890s quite a few surgeons continued to advocate the view that the total thyroidectomy was completely harmless. Most of them drew specifically on the so called geologic-miasmatic theory of goitre causation that had been proposed by the Bristol based surgeon Henry Birkner in 1883.¹⁶³ In his research, Birkner combined the traditional view of endemic constitution as the cause of cretinism and goitre with the new findings of bacteriology. The bacterial agent of these diseases, Birkner conjectured, flourished under particular living conditions that it could find only in the soil of the endemic areas. Birkner explicitly drew parallels to the discovery of the tuberculosis pathogen by Robert Koch in 1882.¹⁶⁴ The promise of disease control associated with bacteriology had such a powerful attraction for the medical profession that occasional attempts to isolate the pathogen causing goitre and cretinism continued far into the twentieth century.¹⁶⁵ From the point of view that goitre and cretinism were the result of one and the same chronic infection that led in the first stage to the development of goitre and in the second stage to cretinoid symptoms, it was

¹⁶² Claude Bernard, *An Introduction to the Study of Experimental Medicine* (New York: Dover, 1957), 98–104. See also: William Coleman, “The Cognitive Basis of the Discipline: Claude Bernard on Physiology,” *Isis* 76 (1985): 49–70.

¹⁶³ Henry Birkner, *Endemic Goitre* (London: Churchill, 1883), v–vi.

¹⁶⁴ *Ibid.*

¹⁶⁵ Bernardino Fantini, “La révolution pastorienne et les théories sur l’étiologie du goitre et du crétinisme,” *Gesnerus* 49 (1992): 21–38.

logical to assume that surgically treated patients only became 'cretins' because they continued to live in endemic areas after their operation. According to this theory, the symptoms of cretinism had nothing at all to do with thyroid insufficiency, and the total extirpation of the gland could be recommended as a means to avoid the recurrence of stage one, i.e. goitre.¹⁶⁶ However, in the light of numerous reports on the occurrence of *cachexia strumipriva* in various regions throughout Europe this hypothesis had become untenable, and observations made in animal experiments provided additional evidence.¹⁶⁷

The question of what led to organ damage in the first place, however, became less relevant.¹⁶⁸ Whether the endemic disease of the thyroid gland was caused mainly by the consumption of unhealthy water, food, or air still remained a mystery and was not of immediate interest, as Horsley declared in 1885.¹⁶⁹ To him, as to others, the disruption of thyroid function was the 'true' cause of these diseases.¹⁷⁰ The focus was now entirely on the organ itself, a single aspect in the pathological process that could be isolated in both experimental and practical procedures, based on arguments about disease causation. All of the factors contributing to these diseases now came together in one concept from which all of the symptoms radiated: cretinism, *cachexia strumipriva*, and cachexia after thyroidectomy in animals were merely symptoms that followed the loss of thyroid function.¹⁷¹

Focussing on the thyroid itself was attractive for several reasons. Not only did it allow the cause of disease to be identified in accordance with the scientific norms of the day, but it also

¹⁶⁶ Turringdon, "The Extirpation of the Thyroid Gland: An Experimental Study," 400; Bornhauser, *Zur Geschichte der Schilddrüsen- und Kropfforschung im 19. Jahrhundert (unter besonderer Berücksichtigung der Schweiz)*, 119.

¹⁶⁷ Turringdon, "The Extirpation of the Thyroid Gland: An Experimental Study," 400.

¹⁶⁸ Ord et al., *Report of a Committee*, 21 (Supplement):87.

¹⁶⁹ Victor Alexander Hayden Horsley, "The Brown Lectures on Pathology," *British Medical Journal* 1 (1885): 212.

¹⁷⁰ Ibid.

¹⁷¹ Ibid., 213. Similar remarks appear in Ord et al., *Report of a Committee*, 21 (Supplement):87.

represented a potential point of departure for treatment: eliminate the necessary cause of a disease and the disease will not occur.¹⁷²

1.5. “OLD” AND “NEW” CRETINISM: FROM ENDEMIC TO SPORADIC CRETINISM

The concept of thyroid replacement therapy came with the corresponding disease entity: thyroid deficiency disease. If researchers wanted to study this disease entity in their laboratories, however, they needed animal models, i.e. they needed to create the disease artificially in animals.¹⁷³ To create such a model, they merged the methods and objectives of experimental physiology, which studied normal life processes, with those of experimental pathology, which aimed at studying diseases. The boundary between experimental physiology and pathology, however, was fluent. According to the physiological view proposed by Claude Bernard, disease was nothing more or other than a variation in normal vital processes caused by changes in the environmental conditions.¹⁷⁴ Normal function and disease were therefore connected, and scientists investigated both normal thyroid function and its disruption with ablation experiments on animals. The impetus for this kind of research came from clinical medicine, and it was only after clinicians had associated a particular clinical picture with the absence of the thyroid by performing their *vivisection humaine* that physiologists even knew which phenomena to observe after organ removal.¹⁷⁵ Hence Schiff's ablation experiments of the 1850s had remained isolated.

¹⁷² Carter, *The Rise of Causal Concepts of Disease: Case Histories*; Carter, “The Development of Pasteur's Concept of Disease Causation and the Emergence of Specific Causes in Nineteenth-Century Medicine,” 536.

¹⁷³ On the animal model, see: Bynum, “‘C'est Un Malade': Animal Models and Concepts of Human Disease.”

¹⁷⁴ Ibid., 400–401. For the concept of disease, see: Owsei Temkin, “The Scientific Approach to Disease: Specific Entity and Individual Sickness,” in *Concepts of Health and Disease: Interdisciplinary Perspectives*, ed. H Tristram Engelhardt, T. H Caplan, and J. J MacCartney (Reading, Mass.: Addison-Wesley, 1981), 247–263.

¹⁷⁵ On this subject in general, see: Borell, “Origins of the Hormone Concept,” 114.

Yet it was not at all easy to develop a convincing animal model. The symptoms of tetany were so prominent in all the animal experiments that the validity of this model for humans remained doubtful.¹⁷⁶ The affected animals, with their heightened nervous irritability and seizures that occurred upon exposure even to the slightest of stimuli, presented practically the opposite picture of the lethargic human patients who suffered from cretinism.¹⁷⁷ This discrepancy remained a weak point in the theory of organ replacement for the thyroid.

We can observe how the redefinition of this disease entity worked in practice by analysing a set of four articles that was published between 1850 and 1887 in Britain. The first was a short case report by the consulting physician to St. Thomas Hospital in London, Thomas Curling, who observed a then astonishing but inexplicable phenomenon. In January 1850, he was called in for a second opinion to the Asylum for Idiots at Highgate. The patient was a ten-year-old girl from Lancashire, admitted to the hospital a couple of weeks ago with signs of severe mental retardation and motor impairment. Curling immediately noted the large head, protruding tongue, and disproportionally large and long limbs, which gave her “countenance ... a marked and very unpleasant idiotic expression.”¹⁷⁸ His initial diagnosis was cretinism.¹⁷⁹ Curling based his reasoning on the patient’s overall expression and the occurrence of two small, symmetrical swellings on each side of the patient’s neck which he identified as goitre.¹⁸⁰ Based on his physical examination, Curling conceded that these swellings were indeed of a goitreous appearance and could well have been indicative for swollen thyroid lobes.¹⁸¹ However, Curling noted that beside the two swellings, he could not feel the thyroid

¹⁷⁶ Schiff, “Bericht über eine Versuchsreihe betreffend der Wirkungen der Exstirpation der Schilddrüse,” 25.

¹⁷⁷ Drobnick, “Experimentelle Untersuchungen über die Folgen der Exstirpation der Schilddrüse,” 156–157.

¹⁷⁸ Thomas Blizard Curling, “Two Cases of Absence of the Thyroid Body, and Symmetrical Swellings of Fat Tissue at the Sides of the Neck, Connected with Defective Cerebral Development,” *Medico-chirurgical Transactions* 33 (1850): 303.

¹⁷⁹ Ibid.

¹⁸⁰ Ibid.

¹⁸¹ Ibid.

gland itself, which ultimately led him to exclude goitre in the patient.¹⁸² Nonetheless, he upheld his initial diagnosis of cretinism. After the girl's death two weeks later, Curling ordered an autopsy to be performed to establish the nature of the growths in the girl's neck. It revealed that the swellings in the neck were composed solely of fat, and "[t]here was not the slightest trace of a thyroid body."¹⁸³

For several decades now, as stated above, British physicians had argued that there existed no necessary connection between goitre and cretinism and thus, Curling was perfectly justified in upholding his diagnosis, despite the apparent absence of goitre and the complete lack of the thyroid gland. However, given the lack of evidence that the condition of the thyroid gland had anything to do at all with cretinism, it is surprising that Curling refers back to the discussion. He concludes his short paper with the remark that "[p]athologists have recently been inclined to view the coincidence of these two affections [i.e., goitre and cretinism] as accidental, or as having no direct relation. In the foregoing cases we have examples of a directly opposite condition ... which may be regarded as tending to confirm the ... connection between cretinism and goitre."¹⁸⁴

The second article to be discussed had been published in 1871 by Charles Hilton-Fagge (1838–1883), then assistant surgeon to the London Hospital's paediatric clinic. Fagge presents four cases and just like Curling, introduces them by making a direct reference to cretinism. However, his ultimate aim was the proposition of a new disease category: *sporadic* cretinism.¹⁸⁵ But, unlike the older form of *endemic* cretinism, the proposed new category was to be associated with the absence of the thyroid body, rather than its hypertrophy.¹⁸⁶ In

¹⁸² Ibid., 304.

¹⁸³ Ibid.

¹⁸⁴ Ibid., 306.

¹⁸⁵ C. Hilton Fagge, "On Sporadic Cretinism, Occurring in England," *Medico-chirurgical Transactions* 54 (1871): 157.

¹⁸⁶ Ibid., 169.

contrast to Curling, who merely hinted at the necessity of further investigation of the thyroid's function in human physiology, Fagge explicates a hypothesis according to which the perceived differences between the *endemic* and *sporadic* forms of cretinism could be explained. Goitre, so his reasoning ran, rather than being the precursor to cretinism should fulfil the positive role of an antagonist to cretinoid affections. He states that, "I have already suggested that in those regions where cretinism prevails endemically, the goitre, which may be regarded as an hypertrophied thyroid body, exerts a similar action in protecting against the more powerful operation of the same cause; and this view appears to me to afford a satisfactory explanation of those relations between goitre and endemic cretinism which have hitherto appeared so difficult of comprehend."¹⁸⁷

This view stood of course in radical opposition to the older notion of goitre as a sign for, and symptom of, cretinism, whilst also challenging the more recent idea of the two conditions as being entirely unrelated. Fagge then began to work out a link with Curling's approach from twenty years earlier. Like his senior colleague, he indicates a connection between cretinism and goitre and summarises the main characteristics of the condition he came to call sporadic cretinism as they presented themselves to him:

- I. The markedly cretinoid appearance of the patient,
- II. The condition is accompanied with the characteristic deficiency in mental powers of endemic cretinism,
- III. Unlike hypertrophy in endemic cretinism, the sporadic variety seems to be associated with hypotrophy of the gland,
- IV. Sporadic cretinism is not necessarily congenital.¹⁸⁸

The last point was especially interesting to him. Up until the publication of his paper, genuine cretinism was understood to be a congenital disease. If, however, so Fagge's reasoning, sporadic cretinism depended on the hypotrophy of the thyroid gland, then it might be

¹⁸⁷ Ibid.

¹⁸⁸ Ibid., 164–166.

possible that the condition could be acquired in the course of the patient's lifespan, due to environmental influences.¹⁸⁹ Ultimately, this remained as much a conjecture on his part as the assumption that goitre in a patient would act like a natural defence against severe cretinism. It is therefore important to note that Fagge essentially frames *sporadic* cretinism like the *endemic* variety, with the main exception of the perceived hypotrophy, rather than hypertrophy, of the thyroid gland.

This theme is still carried further in the third paper I wish to discuss. However, the publication by William Withey Gull (1816–1890) of 1873¹⁹⁰ differs markedly from the aforementioned ones in that he discusses it in adults, whilst borrowing the term *sporadic cretinism* from Fagge.¹⁹¹ Gull was the first to observe and publish five cases in which a condition resembling cretinism was noted and reported in patients in whom the condition appeared not congenitally but who developed the characteristics far into adulthood. Unlike Curling and Fagge, however, Gull does not rely directly on the condition of the thyroid gland. The concept of cretinism, in either its older endemic or the sporadic variety Fagge proposed, remained one related to childhood and pathological conditions of any kind related to the thyroid gland were not known to affect previously healthy and normally developed adult patients.

Both of Gull's main cases were adult women of forty years of age, who came to him as outpatients at Guy's Hospital. Their general physical appearance, which Gull described in detail, appeared cretinoid: their faces were round, the body bulky, and the tongues thick and broad, their voices guttural, and their mental abilities greatly diminished. Had he not heard from their carers that both women had formerly been active and fine-featured, "it would be

¹⁸⁹ Ibid., 166.

¹⁹⁰ William Withey Gull, "On a Cretinoid State Supervening in Adult Life in Women," *Transactions of the Clinical Society of London* 7 (1873): 180–185.

¹⁹¹ Gull mentions five at the beginning of his paper, but analyses only the two cases in outpatients whom he observed and treated extensively. The other three patients he saw "only on one or two occasions." Ibid., 180.

natural to suppose that it was an original defect such as common in ... cretinism.”¹⁹² Gull himself was unsure whether or not he was dealing with cretinoid affections at all. Fagge had only hinted at the vague possibility of sporadic cretinism to appear in adult patients, and endemic cretinism was a congenital disease. Unlike his predecessors Gull saw himself unable to draw inferences from the condition of the thyroid. He states that “the thyroid was not enlarged; but from the general fullness of the cutaneous tissues, and from the folds of skin above the neck, I am not able to state what the exact condition of it was.”¹⁹³ This statement in particular reveals the vague nature of the claims made by Curling and Fagge, since the physical examination of the thyroid by palpation was unreliable. The former was only able to substantiate his claim about the absence of the thyroid gland by aid of the post-mortem examination carried out after his patients’ death, while the latter simply assumed that the thyroid was absent in all of his cases. However, sporadic cretinism, as introduced by the papers of Curling and Fagge, was closely associated with the absence of the thyroid gland. Furthermore, as stated above, the lack of this organ was the primary point of difference from the endemic variety of the disease. It is therefore necessary to discuss Gull’s choice of words in calling the condition “cretinoid.” His own statement remains rather ambiguous: “I have designated this state cretinoid. My remarks are rather tentative than dogmatical, my hope being that once the attention of the profession is called to these cases, our clinical knowledge of them will in proportion improve. That the state is a substantive and definite one, no one will doubt.”¹⁹⁴

Once again, as was the case with Curling, we find the author uncertain about the nature of the condition described. Gull also refrains from pointing towards the thyroid as the main point of reference. Furthermore, he desists from referring to any kind of explanation. He

¹⁹² Ibid., 181.

¹⁹³ Ibid., 185.

¹⁹⁴ Ibid., 184.

rather lets Fagge answer this question, by quoting directly and extensively from the latter's article. Gull's main incentive is Fagge's assertion that sporadic cretinism, due to its dependence on the hypotrophy of the thyroid gland, could potentially be acquired during adulthood. For want of any other explanation, Gull therefore forms a link between his cases and the ones described by Fagge. Furthermore, in anticipation of criticism from physicians familiar with endemic cretinism and its limitation to childhood, Gull defends Fagge's argument and his own observations by declaring that the "statements [by physicians only accustomed to endemic cretinism] are applicable only to endemic cretinism, and therefore the objections from the experience of those who have observed only the endemic cases will be of less value."¹⁹⁵

At this point, short of addressing the aforementioned weaknesses, sporadic cretinism, especially its conception as a disorder directly linked to the state of the thyroid, remained speculative at best. Without an examination of the condition in pathological terms, i.e. one that provided a convincing exposition regarding the perceived symptoms with clinically relevant changes in the patient's body, this disease continued to lack the necessary support to become accepted as a genuine variety of cretinism, and was thus not yet perceived as a clinical entity.

The last article on cretinism to consider here had been published by Victor Horsley in 1887.¹⁹⁶ Although this paper falls outside the temporal scope of this chapter, its inclusion is necessary at this point since the focus here lies with the redefinition of cretinism and goitre in light of the burgeoning thyroid insufficiency concept for which this paper acts as the culmination point. By 1887 the causal relationship between symptoms and organ removal had been

¹⁹⁵ Ibid.

¹⁹⁶ Victor Alexander Hayden Horsley, "Preventing Cretinism? An Englishman's Perspective," *Physiological Review* 3 (1887): 586–626.

demonstrated for artificially created cases of cretinism, i.e. Kocher's *cachexia*¹⁹⁷ as discussed in the preceding section on the invention of surgical thyroid replacement therapy. The idea was now to show that the same was true for 'sporadic' cretinism, a form of cretinism that occurred in adults and children without previously undergoing an extirpation operation. To do this, the disease entity of cretinism had to be readjusted. Horsley therefore explicitly rejected the disease entities created by his predecessors. He thought that earlier investigators had been unable to recognise the specific clinical picture because they did not know the real cause of the disease. The new definition had to be based on the necessary cause of the disease, which, as Horsley wrote, had to be the condition *sine qua non* for the development of genuine cretinism. He counted only those case descriptions in the literature that matched the concept of genuine cretinism; the remaining cases he classified as other disease entities, such as deaf-mutism or idiocy. He applied the same strategy in his epidemiological fieldwork, which bears a striking resemblance to the research practices of Blackie and McClelland discussed in the first part of this chapter. Horsley travelled to the south of England and to Lancashire to examine cases of cretinism in those regions. He wanted to find out whether sporadic cretinism was also correlated with pathological changes in the thyroid gland, and he examined all of those diagnosed as cretins in the places he visited.¹⁹⁸ In Horsley's opinion, most of the patients presented to him were not cretins at all: of the thirty diseased people he was presented with, he accepted only five as cretins; the rest were afflicted with different conditions. The basis of his diagnosis was the similarity of the clinical picture to the complex of symptoms that he had identified in patients who had undergone total thyroidectomies—in other words, similarity to Kocher's *cachexia strumipriva*. This approach was of course very different from what his predecessors had done in their investigations. As a next step, Horsley examined the thyroids of those five cretins and found that three of them had goitre, while two others had no thyroid

¹⁹⁷ Ibid., 596–601.

¹⁹⁸ Ibid.

at all. To Horsley, this discovery confirmed that endemic cretinism, like Kocher's *cachexia strumipriva*, was indeed caused by a lack of thyroid function. He had identified the necessary cause of cretinism, but his findings applied only to cases of cretinism caused by a lack of thyroid function. In other words, *genuine* cretinism was symptomatically identical to postoperative cachexia, but cretinism could only now be identified as *genuine* when it was caused by thyroid insufficiency.

When it came to individual diagnoses, however, Horsley was much more confident than his predecessors: "We have now reached the point, where we can differentiate immediately between a cretin and a patient with another illness, a deaf-mute, a mentally deficient person, or any other kind of idiocy, and where every medical student can make the diagnosis with certainty."¹⁹⁹ He based this newly acquired certainty on his knowledge of the necessary cause: "We now know that the pathological disorder concerns a certain organ, that the affliction of this and only this organ is the cause for the development of genuine cretinism. We can formulate this claim as follows: *we now know the cause of cretinism*, inasmuch as one can speak of a cause when one is able to determine the pathological and anatomical basis of an illness."²⁰⁰ The main focus was now on the disease's direct cause, as located inside the body. Moreover, as Horsley at the end of his paper remarked, concentrating on a single cause contrasted with the pre-1883 accumulation of partial causes: "Instead of a large number of interacting causes in combination, to induce such shocking decline in human beings, it turned out that the failure of a very small gland, hitherto considered insignificant, was able to bring about the clinical picture of cretinism within a few years, even months."²⁰¹

As opposed to his predecessors, who constructed their disease entity on the basis of symptoms in order to find out their causes afterwards, it was Horsley's declared aim to start

¹⁹⁹ Ibid., 606.

²⁰⁰ Ibid., 610–611. Emphasis in original.

²⁰¹ Ibid., 625.

out from the disease's cause and then describe the symptoms. However, much like the earlier work on endemic cretinism, Horsley did not discover a naturally occurring disease entity; rather, he constructed one according to the new concept. The "old" and the "new" cretinism were therefore not identical. The older endemic disease entity did not have organ failure as its necessary cause; this was only true for the new cretinism, which had been constructed on the basis of organ failure. Horsley's redefinition of the disease entity for cretinism and the thyroid deficiency disease in general, serves as just one example of the fact that when doctors and scientists began to attribute necessary causes to diseases they actually had to redefine those diseases first.²⁰²

1.6. THE PROBLEM OF CAUSAL ATTRIBUTION: SPORADIC CRETINISM AND THE THYROID GLAND

As outlined above, sporadic cretinism had been defined as a specific disease entity in Britain by the early 1870s, based on the papers by Curling, Fagge, and Gull. Using an approach typical for medical science at the time, these authors combined clinical data with anatomical-pathological observations. Overall weakness, dropsy, hair loss, decreased mental capabilities, and a thickening of the skin throughout the body marked the disease described. In autopsies, it was observed that patients with this set of symptoms exhibited lesions or, in some cases, a complete absence of the thyroid gland after death. Therefore, as we have seen, attempts were made to make the organ's damage responsible for the clinical picture.

However, at the time, nothing much came of these reports. There was neither a substantial response from the medical community, nor reports on other cases of this condition. Two physiologists, however, attempted to artificially generate the clinically observed symptoms by purposefully destroying the thyroid gland in animals. Gregory Halwood and John Sturges of

²⁰² For this connection between etiological characterisation and necessary cause of disease, see also: Kay Codell Carter, "Ignaz Semmelweis, Carl Mayrhofer, and the Rise of Germ Theory," *Medical History* 29 (1985): 33–34.

the Edinburgh Royal Infirmary noted in 1875 that their laboratory dogs died after an experimental removal of their thyroid glands, and the symptoms they exhibited reminded them of Gull's descriptions of sporadic cretinism.²⁰³ When they furthermore observed that the injection of blood from a rabbit that had died as a result of thyroid extirpation caused the death of healthy animals, but that the transfusion of the blood of a healthy rabbit ensured the survival of animals lacking the thyroid gland, they concluded that a toxic substance, of whatever kind, that was normally neutralised by the thyroid gland accumulated in the blood after the removal of the organ.²⁰⁴ Because other researchers came to very different conclusions, however, it took several years to reach a consensus on the link between thyroid insufficiency and resulting disease symptoms.

One major problem was the establishment of a constantly observable clinical picture. Due to the rarity of cases of sporadic cretinism in Britain, this task was challenging enough when it came to human patients. Developing an animal model for it was an even greater issue, due to the lack of agreement on the cause or even the general course of the condition. Because the symptoms of patients suffering from sporadic cretinism were hard to compare with the symptoms that appeared after the destruction of the thyroid gland in animals, only an experimental animal's actual death could serve as the lone indicator of the gland's absence and the pathologic results.²⁰⁵ Ablation experiments, i.e. procedures that aim to investigate the effects of the removal of specific body parts proved to be controversial, especially regarding the elucidation of causal attributions in diseases. Thus, Curling, Fagge, and Gull's idea to causally link the thyroid gland to sporadic cretinism, as well as Halwood's and Sturgess' attempts at experimental confirmation, was disputed. At first, it looked as though other

²⁰³ Gregory Halwood and John Sturgess, "Physiological Investigations into Sporadic Cretinism, as Reported by Sir William Gull," *Edinburgh Medical Journal* 20 (1875): 946–957.

²⁰⁴ *Ibid.*, 956.

²⁰⁵ Reginald Christopherson, "Physiology of Glands," *The Lancet* 1 (1878): 1015. This suggestion, however, was based on pure conjecture. The thyroid gland, as explained in the previous chapter, had no known function at that time.

injuries caused by these invasive experimental procedures could be responsible for the observed postoperative symptoms and damage to nerve centres in the area of the operation. Damage to certain ganglia, the sympathetic nerve trunk, and such like were often used to explain them.²⁰⁶ On the other hand, some controversies revolved around the question whether experimenters had in fact completely removed the thyroid glands during the extirpation procedures. In this context, it was argued that some animals might have retained accessory tissue located outside the actual organ.²⁰⁷ This was an important matter, because the effects of the failure or lack of the supposed organ function had to be differentiated as fully as possible from those of other influencing factors. Only then could one hope to attribute the observed symptoms to the removal of the organ.²⁰⁸

However, the situation began to change in 1877. A younger colleague of William Gull's, now president of the Clinical Society of London, presented a paper to the society, in which he reported five more cases of what he initially thought to be sporadic cretinism.²⁰⁹ The young physician was William Ord, a general practitioner based in Surrey and who entertained strong links to London's medical establishment. Ord found that in autopsies, two of his five patients showed a marked oedematous condition of the lower layers of their skin, which he attributed to an excess of a mucous substance he called 'mucin.' Strikingly, he mentioned the supposed absence of the thyroid gland in only one patient, and then seemingly in passing. In the

²⁰⁶ These attempts to explain thyroid insufficiency disorders by reference to neurogenic origins continued well into the first decade of the twentieth century. I examine an especially potent example of this in Chapter 4.

²⁰⁷ This idea had first been suggested in 1846 by the Scottish anatomist John Goodsir (1814–1867); see: John Goodsir, "On the Supra-Renal, Thymus and Thyroid Bodies," *Philosophical Transactions of the Royal Society of London* 136 (1846): 633–641.

²⁰⁸ For this, see especially textbooks of diagnosis that urged the students to approach such causal reasoning very carefully, e.g. Andrew Whyte Barclay, *A Manual of Medical Diagnosis: Being an Analysis of the Signs and Symptoms of Disease* (Philadelphia: Blanchard & Lea, 1862); Samuel Fenwick, *The Student's Guide to Medical Diagnosis* (London: John Churchill, 1869); Charles-Éduard Brown-Séquard, *Lectures of the Diagnosis and Treatment of Functional Nervous Affections* (Philadelphia: J.B. Lippincott, 1868).

²⁰⁹ William Miller Ord, "On Myxoedema, a Term Proposed to Be Applied to an Essential Condition in the Cretinoid Affection Occasionally Observed in Middle-aged Women," *Medico-chirurgical Transactions* 61 (1878): 57–78.

following section, I will analyse Ord's paper by paying special attention to the novel pathological disease mechanism he introduced, as this ultimately gave sporadic cretinism its new and lasting name: myxoedema.

1.6. CONCLUSION

In this chapter, we have discovered that the history of cretinism on the British Isles is a richer one than has previously been assumed by historians of endocrinology. Although it is certainly true that the vast majority of cases did not appear in Britain, the country nonetheless underwent at least a revolution in thought regarding the conception of this disease. The proposed reforms, which aimed at preventing an assumed rise in cases, never took root, but the discussion helped to raise the awareness and garnered the attention of a wide spectrum of medical practitioners. Thus, cretinism became the dominant force in paving the way for the burgeoning understanding of the importance of the thyroid gland in general and for the development of the concept of thyroid insufficiency in particular. Thus, as has been discussed in the second part of this chapter, both cretinism and goitre were redefined in relation to the thyroid gland. This process involved not only the growing idea of thyroid insufficiency, but a fundamental transformation of causal attribution, from environmental to internal causes. Although generally in line with the recent development of *necessary disease causation* as suggested by the fledgling discipline of bacteriology, this re-evaluation faced stark criticism from a wide spectrum of the medical community. Kocher's *cachexia strumipriva* posed a far less persuasive argument than he would have wished for. The condition remained 'artificial' in that it was the result of surgical intervention, rather than being a 'naturally' occurring disease. Although it had implications for the general conception of cretinism, it fell short of being able to provide the model character needed for this more fundamental shift.

However, as will be discussed in the following chapter, in Britain, the idea of *sporadic cretinism* in both children and adults would help to foster a process of re-evaluation, which

led to the development of the disease entity *myxoedema*. Although at first a decidedly British phenomenon, myxoedema would provide the necessary impetus that Kocher's *cachexia* had been unable to summon, and thus helped to establish the idea of thyroid insufficiency firmly within the nineteenth-century mind-set of British as well as Continental doctors.

– CHAPTER 2 –

CLINICAL OBSERVATION: WILLIAM ORD AND THE ORIGINS OF MYXOEDEMA

2.1. INTRODUCTION

This chapter investigates how the disease of sporadic cretinism, as discussed in Chapter 1, became reassessed and reframed as the new clinical entity of myxoedema. This investigation begins in 1878 with the publication of the now classic myxoedema article by the London physician William Miller Ord (1834–1902), and ends in 1885, when a committee, commissioned to investigate the subject of myxoedema and appointed by the Clinical Society of London, finished the clinical review of case reports for the disease. The final report also included analyses of laboratory analyses of animal experiments conducted to scientifically explain the associated symptoms. However, as these were not part of the clinical assessment, they will form the subject of the third chapter.

In brief, this chapter investigates the claims made by Merriley Borell, Clark Sawin, and more recently by David Hamilton that the early history of myxoedema—especially the description by Ord and the perceived failure of the clinical part of the *Report on Myxoedema*—is inconsequential for an explanation of the success of the concepts of thyroid deficiency and organ replacement therapy.²¹⁰ In contrast to this, by focussing on clinical observation, I argue that this aspect of the pre-history of the organ replacement therapy and myxoedema is vital for an understanding of the success of both concepts, as the results gained are both reliable

²¹⁰ Borell, “Origins of the Hormone Concept,” 68–69; Sawin, “Thyroid Hormone Therapy: Origins and Early History,” 2; Hamilton, *A History of Organ Transplantation: Ancient Legends to Modern Medicine*, 74.

and accurate. The clinical context not only helped to establish myxoedema as a clinical entity, but also as a viable diagnostic tool and research topic.

The first section focusses on a close reading of Ord's article and shows that, despite his low number of patients, he was successful in establishing myxoedema as a potentially viable clinical entity. The following section then considers the response by the medical community to Ord's paper and addresses the difficulties of determining the pathological mechanisms underlying the disease. Finally, the clinical section of the *Report on Myxoedema* is considered in light of the question why recent historical analysis has classified the clinical work of the committee members as a failure or as irrelevant. The chapter concludes with the argument that the synthesising report of clinical observations on myxoedema played a vital role in its historical development.

2.2. INTRODUCING MYXOEDEMA

The occasion of Ord's novel reinterpretation of the underlying pathological processes of the "sporadic cretinoid affection", that became known as sporadic cretinism, proved to be pure chance. As we have seen in the preceding chapter, cretinism in Britain and on the Continent, was largely perceived as an essentially psychiatric condition brought about by endemic influences stunting the physical and intellectual growth of afflicted patients. This view, although modified, remained largely unchallenged by Curling, Fagge, and Gull, despite their efforts to refocus attention towards the role of the thyroid gland in the development of the condition. It was precisely the juxtaposition of these two premises—the orthodox endemic conception of cretinism with the internally localised view of the thyroid—that accounted for the difficulties of the trio in trying to frame the new diagnostic entity of sporadic cretinism. The hypotheses advanced by these authors were of little practical value to medical doctors and remained a matter of pure speculation. Thus, when William Ord read his paper at a meeting of the Medico-Chirurgical Society on October 23rd, 1877, it was as much a reply to

the aforementioned authors, as it was a collection of case reports and subsequent analysis of a “substantive and definite”²¹¹ medical condition, which he chose to name ‘myxoedema.’²¹² Furthermore, Ord criticised Curling, Fagge and Gull for their insistence on the thyroid gland as the main perpetrator in the condition they described. In the first part of this section, I will focus on the overall structure of Ord’s paper, paying attention to both the recorded symptoms as well as their analysis in terms of the assumed cause. The subsequent part deals with the meta-level of analysis, i.e. the more fundamental question of what Ord was implicitly pursuing in terms of argumentative strategy and justification for his analysis.

Ord’s paper can be divided into two major parts. In the first section he reports on a collection of five case histories of patients whom he believed to have suffered from the condition he later labelled myxoedema. Two of these are elaborately presented at length, while the remaining three serve primarily as brief confirmations of the general results obtained. The second part consists of an analysis of these case histories in terms of the observed symptoms, which are consecutively broken down into what Ord believed to be their respective causes. It must be noted at this point that Ord explicitly denies the possibility of being able to identify the specific causal relationship between myxoedema and somatic lesions—or any other underlying cause for that matter.²¹³ He intended the causal relations in this second part only as possible but informed explanations for the observed *symptoms*. Therefore, the guiding questions for the following analysis are: (1) what kind of evidence does Ord present and is it relevant to other practitioners? In addition, (2) what mode of argumentation is adopted in order to justify the category of ‘myxoedema’? And finally (3), since he responded to the observations made by the three preceding authors, why did he chose to open up an entirely new diagnostic category, i.e. myxoedema, as opposed to sporadic cretinism in adults?

²¹¹ Ibid., 57.

²¹² Ord, “On Myxoedema.”

²¹³ Ibid., 74.

The first patient, and also the only one on whom he carried out a post-mortem examination, was a 54-year-old woman,²¹⁴ who came to Ord as an outpatient at London's St. Thomas's Hospital in 1871, where he served as visiting physician.²¹⁵ The second patient was a woman aged 36 who came under Ord's care at the same institution in 1863.²¹⁶ In both cases, Ord follows the same pattern of presenting the results of his examination. First, he provides a short account of the patient's personal circumstances, followed by a summary of the patient's narrative of the progress of the perceived illness up to the point she came under his care. The third and proportionally longest part comprises a summary of Ord's own examination.

All five patients displayed marked oedema covering the whole body, lethargy, sharply decreased mental capabilities, slow and guttural speech, dry skin that was harsh to the touch, as well as a general impairment of motion. For the purpose of this chapter, I will omit a lengthy reproduction of Ord's symptomatological report and will refer only to the most pertinent parts relevant to this discussion. It is worth noting at this stage that Ord refers to the state of the thyroid gland only once in his report. In his account of the physical examination of the first patient, whilst discussing the amount of subcutaneous fat, he states almost in passing that "the thyroid body could not be felt."²¹⁷ He makes no further reference, or attempts to explain, the state of this organ.

Ord's aim in discussing the symptoms of his patients at great length was to "carry, at least, a suggestion as to the pathology of such cases [of supposed sporadic cretinism] a step further."²¹⁸ Here we find the first indication to the importance of Ord's contribution. Rather than presenting a collection of case reports, like Curling, or additional speculative components, such as Fagge and Gull, he proposes to investigate the condition pathologically,

²¹⁴ Ibid., 57.

²¹⁵ Ibid.

²¹⁶ Ibid., 63.

²¹⁷ Ibid., 60.

²¹⁸ Ibid.

i.e. he attempts to provide both a medically and clinically relevant explanation for the observed symptoms. However, unlike his predecessors, Ord did not focus entirely on the “cretinoid” appearance of the patients, either. For him the sharply decreased mental capabilities, motor impairment, guttural speech, and general oedema were not symptoms of underlying cretinism. In fact, not once does he use the term cretinism—either endemic or sporadic—in his paper. For him, the main symptom suitable to explain all other symptoms was the oedema. Especially in the first case, Ord goes to great lengths in showing how the symptoms developed over the course of the patient’s illness, the only constant being a “gradual swelling of the whole body” worsening from year to year.²¹⁹ His suggestion was that the state of the fibrous structure of the connective tissue as such, accounting for this general oedematous state, is “the essential and common condition of these several cases, and that the nervous disorder [is] definitely consequent thereon.”²²⁰ For Ord, this general oedematous state of the patient was due to the body being subject to “either a jelly-like interstitial matter or [...] tissue in a jelly-like state.”²²¹ Microscopic observation showed that the intermediary cavities of the cutaneous tissues were greatly enlarged, while the fibrous elements were swollen all over the body, resulting in a general separability of the individual fibrils. This condition did not only prevail in the connective tissue of the skin, but also in the sweat and salivary glands, hair-sacs, and the coats of blood vessels, most notably the arteries, which were swollen to almost four times their normal size and subsequently hardened.

Ultimately, so Ord, this condition led to the obliteration of individual arteries, especially capillary ones “for there were many round *areae* which look like arterial structures without a central cavity.”²²² This destructive behaviour could also be found in the liver, the spleen, and

²¹⁹ *Ibid.*, 58–61.

²²⁰ *Ibid.*, 66.

²²¹ *Ibid.*

²²² *Ibid.*

in muscular tissues, particularly the heart,²²³ all of which appeared to be destroyed by the jelly-like oedema. Therefore, the explanation for the dermal oedema, the tender and hardened liver and spleen, the 'absent' thyroid, and the slow movement, both in terms of locomotion as well as speech, is explained by Ord as the result of excessive swelling of connective tissues.

The next point to which he turns his attention is an apparent deficiency in the sensory and nervous system, i.e. the slow reaction to external stimuli and decreased mental activity. In his discussion of these symptoms, Ord states an analogy:

[T]he result of varnishing the skin of animals ... may be noticed for sake of comparison.

When the skin is covered with a gluey insulation material the temperature falls rapidly and death follows. Even if only one sixth of the skin of the whole body is thus insulated the fatal result is produced. This, excluding ideas of poisoning by retained secretion, is due either to rapid loss of animal heat through the varnished surface, or to loss of the tonic influence maintained by exposed periphery.²²⁴

Based on this analogous explanation of the oedematous symptoms, Ord assumes that the oedematous appearance is due to the swelling of the lower layers of the skin, which in turn is due to its infiltration with mucous-yielding material. Ord explains the slow response to external stimuli with reference to the atrophy of the sweat glands, and with pathologic alterations of the nerve-endings in the skin.²²⁵ It is this second explanation that is given more weight in Ord's account. The greatly swollen connective tissue envelopes "the nerve-endings in the skin, so as to be padded and removed from the ready operation of incident impulses,

²²³ Ibid., 67.

²²⁴ Ibid., 69.

²²⁵ Ibid., 67. The assumed insulation of the sweat glands assumed by Ord was the only symptoms thought to be treatable by medication as we will see below.

tactile, thermal, or chemical. They are so placed, therefore, as to receive fewer impulses, and to receive such as reach them more slowly.”²²⁶

This condition of the skin itself, interfering with the natural exposure of nerve-ends to stimuli, appears to Ord in itself as an explanation for “most, if not all, the characteristic nervous phenomena”²²⁷ he described in his symptomatological description. He furthermore proposed that the main cause for the discussed symptoms would be the padding of the “peripheric termination of sensory nerves, and perhaps too of muscular nerves.”²²⁸ It is apparent from these inferences that Ord considered the whole range of symptoms in his five cases to be related, namely via the effects of the “jelly-like” swelling of the connective tissue, consisting entirely of a “mucus-yielding cement by which the fibrils of the white element are held together.”²²⁹ Chemical analysis of this substance, which appeared to have a different composition depending on its location in the body, revealed an excess of mucin in the body parts affected: a mucinous oedema. Accordingly, Ord proposed to “give the name of ‘myxoedema’ to the affection.”²³⁰

The christening of the condition is both obvious and surprising. On the one hand, the proposed name is a reflection of the most striking physical characteristic of the condition, coupled with an exposition of the underlying mechanism. On the other hand, Ord decidedly breaks with Fagge and Gull. Given Gull’s agreement with Fagge on the general underlying disease condition, i.e. sporadic cretinism, it appears peculiar that Ord did not just follow suite by opting for ‘sporadic adult cretinism.’ This would have strengthened his case to provide a pathological explanation for Gull’s cases, just as he had initially set out to do.

²²⁶ Ibid.

²²⁷ Ibid., 68.

²²⁸ Ibid., 71.

²²⁹ Ibid.

²³⁰ Ibid.

In recapitulating his hypothesis, Ord focuses again on neurogenic disorders, and once more argues that the intellectual lethargy and the general slowness of motion are “necessary consequences” of the hindrance of the nervous system to receive external stimuli, due to an encroachment of the dermal nerve-ends with mucin.²³¹ Furthermore, given that myxoedema was framed as a chronic disorder, the nervous degradation tended to be progressive. In the end, death was inevitable due to the almost complete isolation of the nerves from stimuli and the subsequent crushing of glandular structures and vital organs such as the liver, the heart, the kidneys, and the spleen.

Having discussed Ord’s own argumentation, both for his proposal to use the term ‘myxoedema’ to denominate the condition, and for his explanation of the complex set of symptoms associated with the disorder, I will now discuss these issues on a more conceptual level. The first question that springs to mind is: What was Ord attempting to show in his paper? Since Ord was dealing with a pathological condition, he was primarily required to justify it as a clinically recognisable entity. A closer look at how Ord structures his enumeration of symptoms of the cases provides some insight. In the first case, he starts with a very subjective account that was obviously provided by the patient herself:

She had, when first taken ill, been very anxious in connection with the fatal illness of her husband. The first signs of illness were fits of shivering during her work. These were followed by passage of bloody urine, as she believes, on several occasions. Then her hand became “dead,” to use her own expression, when she used her needle; a great addition to her trouble, as she had to work very hard to support herself and her helpless husband. Later on she became “weak-headed,” would be stupefied by a glass of beer at

²³¹ Ibid.

luncheon, experienced a general loss of muscular power, and was “always falling asleep.”²³²

The report of the patient narrative establishes the condition as an illness, as perceived by the patient herself. An idiosyncratic illness, however, with such blurry characteristics, is not necessarily a medical entity, but simply relates to the subjective experience of the patient. Nevertheless, and most importantly, an illness can incorporate a much looser set of symptoms which are not necessarily connected. This strategy on Ord’s side is important, as it enables him to treat the condition that he calls ‘myxoedema’ from a professional perspective. By presenting the set of symptoms the patient is experiencing as an illness, he treats those symptoms as a unity. Secondly, by listing the symptoms chronologically, Ord presents the condition as a progressive disorder.

The second case is much less specific. Here, Ord groups the symptoms, which were identical to those of the first patient, into three general sets: (1) condition of the skin, (3) condition of the nervous system, and (3) general appearance. Therefore, while the second case certainly confirms the symptoms of the first patient, he uses it to introduce the specific clinical picture of myxoedema, which he seeks to prove in the presentation of the three remaining cases. This presentation does not take up more than a short paragraph:

In three other cases I have witnessed a similar combination of symptoms. The patients were all women between forty and sixty years of age. In two of them the urine became albuminous, but not till the dropsical appearance had existed six years in one, and nearly ten years in the other case. All three of these have passed out of my sphere of

²³² Ibid., 58.

observation. But in all, the gelatinous appearance of the skin was well marked; in all there was the slowness of thought and action, hairloss, and slow, painful enunciation.²³³

Here we find the now classic description of myxoedema presented. It lists the quartet of symptoms that is most readily identifiable by an examining physician. Thus, Ord is providing his peers with a basic, although incomplete, list of symptoms which he intends to function as a guide for his fellow clinicians in identifying myxoedema in a given case.

To recapitulate, we find in Ord's paper a trio of case reports, each serving a different argumentative and conceptual need. The first set justifies an understanding of myxoedema as a valid clinical condition, an illness, by revealing in detail the course of the condition. The second set breaks the condition down into sets of symptoms. It is here that Ord starts to systematise the set of symptoms observed in the first case, presents a theory about the nature of the condition and proposes the name of myxoedema. Ord explicitly states that "the name is only intended to represent the condition, and does not profess to involve an explanation of its causes. Whether the mucous œdema be a degeneration, an arrest of development, or an introduction of new material, is not, at present, a question ripe for discussion."²³⁴ The last group of cases, in addition to confirming the first two cases, provided a quick diagnostic reference to myxoedema for the benefit of his peers.

The question remains whether Ord's myxoedema is related to sporadic or endemic cretinism at all. In contrast to the earlier publications by Curling, Fagge, and Gull, Ord does not focus his efforts on relating the state of the thyroid to cases of cretinism, either sporadic or endemic. Nor, as we have seen, does he set his mind on this organ to explain and classify the symptoms. Instead, he creates an entirely new diagnostic entity by concentrating his efforts on pathologic changes in connective tissues and the resulting neurological changes in the

²³³ Ibid., 65.

²³⁴ Ibid., 74.

patient. The link in the chain of his reasoning is the excess of mucin, the denominating substance of his proposed syndrome, which could be called upon to explain all the perceived signs and symptoms of the disease. Thus, with the publication by Ord, we finally have what neither Curling, nor Fagge and Gull were able to provide: a pathologically relevant exposition of the underlying pathologic changes; and with it an ability to explain the symptoms of the formerly elusive condition 'sporadic cretinism'. Ord's reframing and renaming of the condition as myxoedema was not strictly necessary, but it enabled him to break with the previously strict focus on cretinism both conceptually as well as clinically.

Ord's account of the new diagnostic entity myxoedema relied heavily on his own observations and the first-person reports of some of his patients; furthermore his own interpretation, explanation, and assessment of the constancy of symptoms, and, finally, the observed changes in the condition of the patient. This is, of course, the core of clinical work and is intended to provide a gradually more nuanced understanding of the condition in question. Thus, it is not self-evident that Ord as a clinician simply wanted to provide a single definition of myxoedema on the basis of five cases, as some authors have suggested.²³⁵ The open question of causation and the focus on the introduction of a set of symptoms to identify myxoedema strongly suggest otherwise.

In the next section, I will describe and discuss the initial reception of Ord's ideas by the medical community, in Britain and internationally. This will begin to pave the way for an assessment of the development of the concept of myxoedema, based on the aforementioned method of observation, explanation/interpretation, and symptom analysis, which will lead us

²³⁵ Borell briefly mentions myxoedema in her analysis of the origins of endocrinology and states that Ord's paper proved to be the definite account of the disease, thus ultimately ruling out any competing views; see Borell, "Origins of the Hormone Concept," 40–41. Clark Sawin also bases his analysis on the same assumption: Clark T. Sawin, "Defining Myxoedema and Its Cause," in *Report of a Committee Nominated December 14, 1883 to Investigate the Subject of Myxoedema; Being a Supplement to Volume 21 of Its Transactions; Facsimile Edition* (Boston: The Francis A. Countway Library of Medicine, 1991), 1–14.

on to chapters three and four. It will become clear that myxoedema developed into a viable clinical entity not because of the disease mechanism put forward in Ord's paper, but notwithstanding it.

2.3. NEGOTIATING MYXOEDEMA: ESTABLISHING THE COMMITTEE OF THE CLINICAL SOCIETY

Looking back at Ord's paper, we can characterise his contribution to the debate on sporadic cretinism and myxoedema to be four-fold: first, he provided an overview of the symptoms of what was then known as sporadic cretinism; second, he arranged for the first autopsy of an adult with the disease; thirdly, he reassessed the clinical picture based on his post-mortem examination; and finally, in light of his results, Ord gave it a new, specific name: myxoedema.

A clear set of symptoms, the memorable name, and the ability to perform a biochemical test to determine the presence of excessive mucin to make a diagnosis attracted immediate attention, and case reports soon began to appear in the leading medical journals.²³⁶ Ord publicised the disease, and of course himself, by lecturing on it at medical meetings. In his lectures, he emphasised his belief that an excess in mucin itself, produced by an as of yet unknown mechanism, was responsible for all the signs and symptoms including poor brain function.²³⁷

²³⁶ Over forty such reports of cases of myxoedema appeared between 1879 and 1883. For reasons of brevity, I will here only provide a small sample, as others will be discussed below: Dyce Duckworth, "On a Case of Myxoedema, or Universal Mucinoid Degeneration of the Connective Tissue of the Body," *Transactions of the Clinical Society of London* 8 (1878): 97–98; J. Lediard, "Case of Myxoedema," *Lancet* 1 (1879): 366; W. Inglis, "Two Cases of Myxoedema," *Lancet* 2 (1880): 864; J. Hopkins, "Case of Myxoedema," *Lancet* 2 (1881): 1021; William Gowans, "History of a Case of Myxoedema," *British Medical Journal* 1 (1882): 772–773; T. R. H. Clunn, "Myxoedema Following Haemorrhage," *British Medical Journal* 1 (1883): 312.

²³⁷ William Miller Ord, *On Some Disorders of Nutrition Related with Affections of the Nervous System (Neurotic Dystrophies)* (London: Harrison and Sons, 1884); Ord, "The Present State of Myxoedema: Being a Discussion of the Relevant Clinical Signs of the Disease"; William Miller Ord, "Clinical Lecture on Myxoedema," *British Medical Journal* (1878): 671–672.

In addition, the disorder was being described widely in the United Kingdom in case reports that were often accompanied by typical photographs or woodcuts; the condition was also rapidly recognised on the Continent and in the United States, with case reports coming from New York, Syracuse, Chicago, and Louisville.²³⁸ However, the term myxoedema was not universally favoured. In Paris, Jean-Martin Charcot (1824–1893), most famous for his contributions to the field of neurology, preferred the term *cachexie pachydermique*,²³⁹ which restricted the name for the condition to the visible clinical picture— in this case a wasting condition with thick skin—without implying an underlying pathological mechanism as was the case with myxoedema.²⁴⁰ Ord's name for the disease, however, stuck; it had a tendency to crystallise in the minds of physicians and medical researchers a particular diagnosis as well as a method of arriving at it in cases of patients previously thought to be only vaguely ill.²⁴¹

However, controversy arose as to the immediate cause of myxoedema, with most physicians assuming that the defect had to lie with the central or sympathetic nervous system.²⁴² Nevertheless, Ord persisted in his own assessment. For the time being, no position gained the consensus of the medical community, but an agreement ensued that the condition was indeed a distinct entity and, whether or not an excess of mucin was responsible for the set of

²³⁸ W.A. Hammond, "On Myxoedema, with Special Reference to Its Cerebral and Nervous Symptoms," *St Louis Clinical Record* 7 (1880): 421–425; A.C. Mercer, "Myxoedema," *Medical Record* 19 (1881): 421–425; J. W. Holland, "Remarks Upon a Case of Myxoedema," *American Practitioner* 26 (1882): 129–134; J. A. Robinson, "Myxoedema," *Chicago Medical Journal and Examiner* 47 (1883): 467–473.

²³⁹ Jean-Martin Charcot, "Myxoedème, cachexie pachydermique ou état cretinôide," *La Gazette de l'hôpital* 1 (1880): 73–75; G. Ballet, "Cachexie Pachydermique (Myxoedème, des auteurs anglais)," *Progrès Médicale* 8 (1880): 605–606; Georges Ridel-Saillard, *De la Cachexie Pachydermique (myxoedème des auteurs anglais)* (Paris: A. Delahaye & E. Lecrosnier, 1881); Léon Brachet, *Observations de cachexie pachydermique de Charcot, myxoedème crétinoïde de sir William Gull et de Ord, par le Dr Brachet. Lecture faite au congrès des Sociétés savantes, à Aix-les-Bains, le 25 septembre 1882* (Paris: Gêrente, 1883).

²⁴⁰ Charcot was a respected medical scientist, clinician, and teacher at the famous Pitié-Salpêtrière Hospital in Paris. He was also no stranger to the introduction of new disease entities. He contributed to the understanding of Parkinson's Disease and introduced the new clinical entity of Multiple Sclerosis; see: Karl Ekbom, "The Man Behind the Syndrome: Jean-Martin Charcot," *Journal of the History of the Neurosciences* 1 (1992): 39–45.

²⁴¹ Sawin, "Invention of Thyroid Therapy."

²⁴² An exposition of these neurogenic accounts is provided in John Gimlette's book on myxoedema, see: John D Gimlette, *Myxoedema and the Thyroid Gland* (London: J.&A. Churchill, 1895), 70–73.

symptoms associated with it, myxoedema was the favoured term. Some ostensible success with therapy also appeared. By 1883 a few patients seemed to improve when prescribed arsenic, nitroglycerin, strychnine, quinine, etc; that is, with stimulants, which seemed to be the logical choice given the prevailing lethargic condition of the patients. The defect in sweating, which Ord described in his paper, and which he deemed indicative of mucinous degeneration of the sweat glands, was initially treated with jaborandi, an extract of the rutaceous plant *Pilocarpus jaborandi*, widely used as a glandular stimulant and diaphoretic, or pilocarpine, jaborandi's main alkaloid.²⁴³ As a result of this treatment, some patients showed some increased perspiration, and the treatment was considered a success. Overall, however, no single course of treatment seemed to work well enough in all patients.

As we have seen in the previous chapter, four years after Ord's publication, during 1882 and 1883 in Switzerland, where endemic cretinism and often enormous goitres were relatively common, the attention turned towards the thyroid gland, due to the experimental operations carried out by Theodor Kocher in Berne and Jacques-Louis Reverdin in Geneva. However, the often devastating results of total thyroidectomies, leading to what Kocher, termed *cachexia strumipriva*, which were performed as treatment for cretinism and goitre, led the two surgeons to apply this procedure in only the most desperate of cases. Neither of them seemed to have been aware of the English disease myxoedema, and neither was able to attribute the unfortunate results of thyroidectomies to thyroid deficiency—as the concept of the latter did not yet exist.²⁴⁴ Thus, while both Reverdin and Kocher attempted to modify their

²⁴³ Gowans, "History of a Case of Myxoedema"; J. R. Heron, "Case of Myxoedema in a Man," *British Medical Journal* 1 (1882): 89; Thomas Oliver, "Clinical Lecture on Myxoedema," *British Medical Journal* 1 (1883): 502–504.

²⁴⁴ The mere association of thyroidectomies with *cachexia strumipriva* was insufficient to prove causality between the disease and the function of the thyroid gland. See Chapter 1 for a discussion of the reasons.

surgery, they did not pursue the nature of the defect or associate a functional relationship with the thyroid gland.²⁴⁵

One member of the Clinical Society of London, however, came across the procedures carried out in Switzerland. Felix Semon (1849–1921), an up-and-coming otolaryngologist based in London who was born and trained in Prussia but had immigrated to the United Kingdom, saw Theodor Kocher's report shortly after it was published. The results had been presented as a major speech on the unfortunate consequences of thyroidectomy in April, 1883, to the German Society for Surgery.²⁴⁶ Being familiar with the account of his colleague Ord, Semon recognised a certain similarity between *cachexia strumipriva* and myxoedema, but suspected that Kocher was not familiar with the new English disease entity. Semon called upon Ord to send a note of introduction to Kocher, outlining his thoughts and results, and, more importantly, to enclose a picture of one of his myxoedematous patients.²⁴⁷ Upon reviewing the material, Kocher replied: "There cannot be the slightest doubt of the analogy of Myxoedema and cachexia strumipriva. I was not aware of it before [...]"²⁴⁸ By June 1883, Reverdin had also made the possible connection between the two conditions and proposed to give the post-operative disease the name "myxoédème opératoire."²⁴⁹

Later the same year, the Clinical Society of London's meeting of November 23rd, 1883 was almost entirely given over to myxoedema.²⁵⁰ The president, the Scottish physician and pathologist Sir Andrew Clark (1826–1893), had asked Semon to present the encounters

²⁴⁵ Tröhler, "Die Wechselwirkung von Anatomie, Physiologie und Chirurgie im Werk Theodor Kochers und einiger Zeitgenossen"; Urs Boschung, ed., *Theodor Kocher 1841-1917* (Bern: Hans Huber, 1991); Oliver Isepponi, Valentin Huwiler, and Urs Boschung, "Theodor Kocher's Surgical and Clinical Case Presentations," *Bulletin of the History of Medicine* 78 (2004): 192–194.

²⁴⁶ Kocher, "Über Kropfextirpation und ihre Folgen."

²⁴⁷ Donald Harrison, *Felix Semon 1849-1921: A Victorian Laryngologist*, Eponymists in Medicine (London: Royal Society of Medicine Press, 2000), 92–93.

²⁴⁸ F. G. D. Drewitt, Felix Semon, and William Miller Ord, "A Typical Case of Myxoedema," *British Medical Journal* 2 (1883): 1073.

²⁴⁹ J. L. Reverdin and A. Reverdin, "Note sur vingt-deux operations de goitre," *Revue Médicale de la Suisse Romande* 3 (1883): 169–198, 233–278, 309–364.

²⁵⁰ Drewitt, Semon, and Ord, "A Typical Case of Myxoedema."

between himself, Ord, and Kocher. Semon described Kocher's awkward outcome and tentatively advocated the idea that since the "absence or probably complete degeneration of the thyroid body" was the one thing in common to cretinism, myxoedema, and the thyroidectomy outcome, there might be a possible relation between the condition of the gland and those diseases.²⁵¹

Eight other society members commented on Semon's ideas, including Ord and Sir William Gull, but no consensus was reached and serious scepticism ensued about Semon's proposition. Gull simply denied the fact that the thyroid, an organ that seemed to be of no great importance to the body's metabolism, could have such an important part in pathology, whilst Ord, not without self-interest, pressed for his own mechanism of the mucin oedema.²⁵² The president left the discussion at this, but added that both Ord's own theory about the pathogenesis of myxoedema and the developments in Switzerland in the wake of total thyroidectomies might warrant the appointment of a specialised committee to investigate the matter further.²⁵³ Yet, only three weeks later, Clark did exactly that and appointed a committee of twelve,²⁵⁴ comprised of eleven clinicians (William Ord, John Cavafy, James Goodhart, Felix Semon, William Hadden, Arthur Durham, Rickman Godlee, Warrington Harvard, Sydney Jones, Stephen Mackenzie, and Pugin Thornton), and an experimental scientist (Victor Horsley)²⁵⁵, whilst the chair was taken by William Ord.²⁵⁶

²⁵¹ Clinical Society of London, "Minute Book of the Clinical Society of London," 1888 1877, 27, ClinSoc 16678.13 T23, Royal Society of Medicine.

²⁵² Clinical Society of London, *Transactions of the Clinical Society of London*, vol. 16 (London: Longmans, Green, & Co, 1883), 207–211.

²⁵³ *Ibid.*, 16:211.

²⁵⁴ The official denomination of the committee was "Committee of the Clinical Society of London, Nominated December 14, 1883 to Investigate the Subject of Myxoedema." For reasons of brevity, I will henceforth refer to it as "the Committee."

²⁵⁵ Horsley joined the Committee one year later, in 1884.

²⁵⁶ In this chapter, I will be mostly concerned with the pathological and clinical accounts. The laboratory analyses of Horsley will form the core of Chapter 3.

2.4. ESTABLISHING THE CLINICAL PICTURE OF MYXOEDEMA

How the clinical Committee approached myxoedema at first is not entirely clear. The first year seems to have been taken over by case reviews and an analysis of the symptoms and course of the disease. As first-hand observations proved to be almost impossible, as only two cases of the condition had been reported in the vicinity of London, this review was by and large based on published accounts following in the wake of Ord's article. When exactly this evaluation was carried out is unknown. Regarding possible modes of treatment for myxoedema, it was conceded that jaborandi and pilocarpine did indeed exert beneficial influences, as eleven of eighteen patients so treated were reported to have shown some improvements.²⁵⁷ After reviewing twenty-two autopsy reports, the clinicians concluded regarding the condition of the thyroid, that it appeared reduced in size in about twenty-five per cent of the cases, and that in those it seemed to have been converted into pure fibrous tissue, which contained masses of round cells.²⁵⁸ Ord introduced these results at the first meeting of the Clinical Society in 1884 and argued that Semon's idea regarding thyroid involvement in the condition seemed to have been refuted "once and for all. If, as my valued colleague has stated, there would indeed be a link in the pathology of the conditions reported by Dr. Kocher and myself, this link will not be the thyroid body."²⁵⁹

Regarding the attempt to establish a universal clinical picture of myxoedema by the Committee, the results gained by Ord and published in his 1878 article, played a fundamental role. In the end, Ord used the preliminary results of the clinical sub-committee as an argument partly in favour of his own pathogenetic account. He postulated, as discussed above, that the skin over-produced a mucous-like substance called mucin, which led to serious

²⁵⁷ Ord et al., *Report of a Committee*, 21 (Supplement):22.

²⁵⁸ Ibid., 21 (Supplement):46.

²⁵⁹ Clinical Society of London, "Meeting, April 1884," *Transactions of the Clinical Society of London* 17 (1884): 39.

damage throughout the organism.²⁶⁰ Thus alerted to the possible existence of excessive mucin, the committee began to investigate the physiological effects of this substance in the published case reports.

Cavafy, Semon, and Hadden, for example, reviewed the published reports of myxoedematous patients and found to their surprise that only five out of the 117 reports they surveyed mentioned a noticeable thickening of the skin.²⁶¹ Discouraged by those findings, they began to gather cases which were still under investigation by physicians in the London area, but two years and 14 cases later, they had to conclude that an apparent excess of mucin was only observable in about four per cent of genuine myxoedema cases. In 1884 the trio resorted to a different tactic. They published a short report in the *Lancet*, outlining their failure to recognise the existence of mucin in myxoedematous patients and asked fellow British physicians for their assistance, as it would be possible “that the general practitioner, who is familiar with the idiosyncratic progression of his case [of myxoedema], might be able to shed light on the thesis that the postulated mucin oedema be a mere stage in the overall course of the condition.”²⁶² The impetus for this brief publication came from William Ord himself, because he was unsatisfied by the preliminary findings of his committee members. He held the opinion that the low percentage of cases in which a mucin oedema could be detected undermined his own theory about myxoedema. Although not convinced himself, he entertained the idea that mucinous oedema might be a stage, or its appearance might oscillate over the course of the disease, thus making it potentially difficult to detect or, if indeed observed, disregarded as unrelated.²⁶³ Ord’s paper on myxoedema had been the first to advocate and present the use of mucin as a precisely measurable effect in the diagnosis of

²⁶⁰ We have encountered his initial argument before in this chapter in section 2.2.

²⁶¹ W. B. Hadden and John Cavafy, “The Symptoms of Myxoedema,” *British Medical Journal* 1 (1883): 189.

²⁶² W. B. Hadden et al., “Myxoedema: The Question of Mucin,” *Lancet* 2 (1884): 1077.

²⁶³ William Miller Ord, “Ord to Hadden,” April 16, 1887, Wellcome Manuscript Collection.

myxoedema, but the cases published in his article's wake never mentioned the oedema itself. The call for help remained unanswered. The physicians officially confirmed their lack of positive results in their final report to the Clinical Society in 1888.²⁶⁴ Felix Semon, of course, saw his own idea about a link between myxoedema and the thyroid gland as a possibility for further investigation by the Committee. He communicated his desire to "investigate the thyroid body's connection to the disorder" to Ord in December 1884, but his request was denied.²⁶⁵

The second task of the clinician sub-committee was the investigation of symptoms as well as potential courses of treatment. Ord had provided the template for myxoedema's diagnosis in 1878, but it was easier to diagnose the disease than to treat it. Nevertheless, without treatment, the course of the condition was fatal. The committee could agree that the symptoms of myxoedema were far more wide-ranging than the apparent inability to sweat, the dropsical appearance, and general physical weakness. The blood vessels of the lower extremities of an untreated myxoedematous patient seemed particularly liable to be damaged. Long-term sufferers often developed blindness and severe infections of the skin, often accompanied by gangrene. All wounds healed badly. They also seemed to have a much lowered tolerance to communicable diseases of all kinds and were thus as likely to die from pneumonia as by the deterioration of their myxoedematous condition. Moreover, female patients were rarely able to carry a pregnancy to full term. The clinicians also introduced more wide-ranging indications for myxoedema. The long list included nervousness, lethargy, exhaustion, dizziness, anaemia, insomnia, hot flashes, depression, abdominal pain, osteomalacia, and cardio-vascular deterioration.²⁶⁶ Mental and neurological problems also

²⁶⁴ Ord et al., *Report of a Committee*, 21 (Supplement):59–60.

²⁶⁵ Clinical Society of London, "Minute Book of the Clinical Society of London," 86.

²⁶⁶ Ord et al., *Report of a Committee*, 21 (Supplement):18–20.

featured prominently, ranging from poor memory and depression to attempted suicide.²⁶⁷ Even outright psychiatric diagnoses such as *dementia praecox* and *manic-depressive madness* appeared on the list.²⁶⁸

Behind the diagnosis of *dementia praecox*—about the same illness that was later reconceptualised as schizophrenia—was the theory of somatic pathogenesis: the patho-neurologist on the committee, William Hadden, was an advocate of the theory that afflicted patients carried an “unknown, but malicious substance” in their blood, which was directed against their nervous system.²⁶⁹ The resulting nerve degradation then led to certain pathological changes in the nervous system that underlay the psychiatric symptoms, which, Hadden thought, strikingly resembled those of myxoedema.²⁷⁰

The extensive list of symptoms associated with myxoedema notwithstanding, by the end of the second year, the Committee had narrowed down the attribution of the observed therapeutic effects to the stimulants of jaborandi and pilocarpine, observations that, on the outset, seemed to be confirmed by several case and treatment reports.²⁷¹ The committee now aimed directly at identifying the surest way of therapy. Regardless of the setbacks they experienced when it came to positively identifying the postulated mucin oedema, it still seemed obvious to them to explain myxoedema as the result of the effects of mucin encasement of nerve ends, as Ord had hypothesised in 1878, and to try and find a therapy for patients along those lines. However, this strategy also proved to be difficult. When viewed in perspective, the results gained from stimulants, be they glandular as jaborandi, or nervous stimulants like nitro-glycerine, strychnine, and arsenic, were utterly disappointing. Large

²⁶⁷ Ibid., 21 (Supplement):22.

²⁶⁸ Ibid., 21 (Supplement):24.

²⁶⁹ W. B. Hadden, “The Nervous Symptoms of Myxoedema,” *Brain* 5 (1883): 190.

²⁷⁰ Ibid., 196.

²⁷¹ Cecil F. Beadles, “The Treatment of Myxoedema and Cretinism, Being a Review of the Treatment of These Diseases with the Thyroid Gland, with a Table of 100 Published Cases,” *Journal of Mental Science* 39 (1898): 343–355; 509–536; *British Medical Journal*, “Myxoedema and Cretinism,” *British Medical Journal* 2 (1884): 1028–1029; Oliver, “Clinical Lecture on Myxoedema.”

doses of jaborandi were, however, still administered in cases of myxoedema up until 1890. The Committee recommended improving the therapeutic effect with a diet high in quantities of fat and carbohydrates, as “the active principle of the stimulant is directly enhanced by the body’s ability to digest it.”²⁷²

By this time, Ord showed dissatisfaction with the results of the clinical sub-committee. Clearly, the data generated were not in agreement with what might be expected if his initial assessment of the disease’s pathogenesis was correct. Thus, in 1885, he conceded to Felix Semon and approved a survey of surgeons all over Europe with the aim to assess how many of them had actually seen myxoedematous symptoms after total thyroidectomies as in Kocher’s reports. Even though, if successful, this survey would have undermined Ord’s mucin oedema concept, at this point, both the members of the Committee and the Clinical Society were desperate for useful information of any kind.²⁷³ Semon undertook this task by mailed questionnaire, including a typical photograph of a myxoedematous patient in February 1885. Here again, there was more, not less, uncertainty. After he received 98 responses, Semon took the sixty-nine usable replies, i.e. those with enough data to determine whether or not there was a total thyroidectomy and subsequent myxoedematous symptoms. In contrast to Kocher’s patients, however, all of whom either developed the striking symptoms or suffered a relapse of goitre which indicated incomplete thyroidectomy, only about one-third of the total usable replies Semon received had the untoward outcome. And only one known example was reported to have occurred in the United Kingdom. While there were probably good reasons for this failure to confirm the hypothesis of a link between the absence of the thyroid gland and the onset of myxoedema, Semon had little choice but to state that the data were in fact equivocal and certainly did not come out as expected.²⁷⁴

²⁷² Ord et al., *Report of a Committee*, 21 (Supplement):83.

²⁷³ Clinical Society of London, “Minute Book of the Clinical Society of London,” 217.

²⁷⁴ Ord et al., *Report of a Committee*, 21 (Supplement):93.

Overall, the outcome of the attempt to provide a recommended course of therapy was disappointing. Despite the reiteration of the potentially, yet irregular, beneficial effects of stimulants, only “warmth” was advocated. The clinicians on the Committee closed their brief account with the remark that any conditions under which remissions might occur, either naturally or through the use of therapy, might become better understood once the causal agent of the disease would be known. Until then, the existent data prevented the Committee to “come to a certain conclusion” with regard to a clinical assessment and therapeutic recommendation.²⁷⁵

This brings us back to one of the main themes of this chapter, observation, understood along the lines of Pickstone’s first way of knowing, i.e. natural history. Up to this point, the members of the Committee had observed the cases reported in the medical literature which resulted in the creation of lists of symptoms for myxoedema, the general course of the disease, and potential treatment methods. Contrary to Ord, who had based his original assessment of myxoedema on five cases, the Committee drew their conclusions from a much wider pool of 119 cases. Thus, to assess their performance up to this point as a failure, due to their inability to significantly add to the knowledge about the disease, would be premature.

The main reason is that in order to be valuable, clinical observation must be both accurate and reliable. Reliability in this case was achieved by the analysis of reports of more than one observer, and by results that are in principle reproducible, or re-observable. Reports that were not reproducible at this point in time were of only very limited reliability, even though they might become so at some point in the future. The Committee was successful in this respect. For the first time, they brought together the available case reports, which, with all their idiosyncrasies and at times conflicting data, painted a much richer picture of myxoedema than Ord could ever have hoped for from his observations alone. Thus, to say

²⁷⁵ Ibid., 21 (Supplement):182.

that no results were achieved in the clinical description of myxoedema is inappropriate. The symptoms of the disease had been consolidated, combed through for irrelevancies, and synthesised into a unified account.

Also, in order to be viable, observations need to be carefully conducted, so that extraneous factors are ruled out to the greatest extent possible. Thus, observers needed to report their findings precisely. It is one thing to report that the patient's skin showed no significantly increased levels of mucin, but quite another to state that 25g of skin contained 0.3mg of mucin, i.e. 0.012% of the sample's mass. As this level of precision was unobtainable by the Committee at this time, they opted to present their conclusions in a tentative and conservative manner, namely by stating their inability to reach certain conclusions. Although not precise, their conclusions were nevertheless rigorously obtained and formulated. Observations that are obtained in such a manner satisfy the requirements of a medical investigation far better, like the Committee's into myxoedema, than those that do not meet the requirements of accuracy and reliability.

Overall, this achievement of the Committee satisfies Pickstone's first way of knowing, natural history. The Committee report consisted of the description and classification of things as they then were and have come to be. Pickstone argues that the more enquiry is concerned with complexity or singularity, the more the observers tend to adopt the natural history way of knowing. Ord and his fellow members of the clinical side of the Committee fit this category, as they did surveys, described changes in the diagnosis, classified as well as tabulated their findings.

2.5. CONCLUSION

This chapter seemingly presents the simple story of how myxoedema, both as a concept and as a clinical entity, was introduced to the medical community between 1878 and 1884.

However, the cautious results obtained by the clinicians on the Committee mean that this is only a tentative conclusion. The recent historiographical representations of the developments considered in this chapter seem to show a misunderstanding of the clinical work accomplished during this period. Clinical observation, when done accurately and reliably, is a necessary aspect of the understanding of disease, and the key actors in this chapter did adhere to this standard. Thus, myxoedema, although neither completely understood, nor entirely framed, became a viable, although tentative, tool for the diagnosing physician as well as the laboratory scientist.

The Committee now had to resolve the question why no excess mucin occurred in the majority of patients, thus finding an explanation for Ord's potential mischaracterisation of the disease. On the other hand, they had to address the issue why less than half of the patients with total thyroidectomies eventually developed myxoedematous symptoms, thus challenging Semon's link between the lack of the thyroid and the onset of myxoedema. As we will see in the next chapter, answers to these questions were expected from the newcomer to the Committee, the medical scientist Victor Horsley, who was appointed on the recommendation by Ord and Semon in August 1884, and who was to make major contributions to the laboratory analysis of myxoedema.

– CHAPTER 3 –

SCIENTIFIC ANALYSIS: VICTOR HORSLEY AND THYROID REPLACEMENT

3.1. INTRODUCTION

In order to understand how laboratory analysis strengthened the results gained by the Committee for the Investigation of Myxoedema, this chapter focusses on Victor Horsley's experimental investigations into thyroid ablation experiments in animals. The chapter is mainly based on the work carried out between 1884 and 1888, but extends its focus into 1891 in order to investigate the wider reception and conclusions gained by Horsley regarding the proof of a causal link between myxoedema and the loss of the thyroid gland. The main aim of this chapter is to understand how scientific analysis contributed to the concept of myxoedema, but still proved insufficient for a complete understanding of the disease. It also challenges the recent assessment by historians of medicine, most notably Thomas Schlich and David Hamilton, that the rationale of proving a causal link between thyroid ablation and the occurrence of myxoedematous symptoms by way of its reversal, i.e. thyroid transplantation or grafting, was ultimately a failure.²⁷⁶ I conclude that, although the results of both the Committee and Horsley were indeed inconclusive, they were open-ended and thus played an important part as the necessary foundation for the development of the experimental thyroid replacement therapy concept, which will be discussed in Chapter 4.

²⁷⁶ Schlich, *The Origins of Organ Transplantation: Surgery and Laboratory Science, 1880-1930*, 57–58; Hamilton, *A History of Organ Transplantation: Ancient Legends to Modern Medicine*, 97–98.

By and large, this chapter draws from Pickstone's second way of knowing, i.e. analysis. This way of knowing is characterised by seeking understanding in breaking the phenomena under investigation down into their constituting elements. In this case, the focus was not on surveying and classifying the observed effects of myxoedema and the supposed changes in the thyroid gland as discussed in the preceding chapter in relation to Pickstone's concept of natural history, but on the systematic analysis of the cause of the affliction in relation to the thyroid.

The first section describes the attempts to develop a pathological concept for the thyroid gland, whilst the following section discusses the resulting redefinition of the previously distinct clinical entities of myxoedema, *cachexia strumipriva*, and (sporadic) cretinism into one unified entity, myxoedema. Although it may be objected here that the unification of the three clinical entities into one, myxoedema, goes beyond Pickstone's historiographical notion of analysis, this process was not the result but a vital aspect of this analytical stage, as it provided the conceptual justification for Victor Horsley's work on the physiological analysis of pathological changes in the thyroid gland. Thus, the third section goes beyond the scope of the Committee and investigates Horsley's efforts to substantiate the assumed causal link between thyroid dysfunction and the new myxoedema by way of ablation and transplantation experiments in animals, as well as the responses by his fellow experimental researchers. The final part of this chapter briefly discusses the conclusions reached by the Clinical Society's Committee and assesses whether the *Report* truly proved to be inconsequential for the development of the medico-scientific understanding of myxoedema. As indicated above, focussing on Pickstone's analytical way of knowing, I will argue that the *Report* actually provided the basis for further investigations into both myxoedema as a curable disease, and the concept of thyroid replacement therapy.

3.2. DEVELOPING A PATHOLOGICAL CONCEPT FOR THE THYROID

Clinical observation by itself proved to be insufficient for an understanding of myxoedema, as the cautious conclusions from the clinicians of the Committee testify. By the end of 1884, Ord found himself struggling to justify the expense and hours of work he invested for the Clinical Society.²⁷⁷ The president acknowledged the difficulty of the research but the Society's council questioned the feasibility of further work to be undertaken. The Committee Chair conceded that the activities over the past year had been focussed on demonstrating his own hypothesis of myxoedematous symptoms being caused by excessive mucin in the patient's body, but that no confirmation resulted from the cases reviewed. Almost as a last resort, the surgeon Rickman Godlee (1849–1925) suggested that laboratory investigations into the phenomena caused by myxoedema might shed light on some of the Committee's most pressing questions. He also reemphasised the need to take Semon's earlier idea about the link between *cachexia strumipriva* and myxoedema seriously and to investigate the relationship between the loss of the thyroid gland and the two conditions.²⁷⁸ However, the Society not only lacked the necessary equipment and laboratory space, but also a suitable experimental physiologist. Nevertheless, help came unexpectedly.

Felix Semon had visited Edward Schäfer's (1850–1935) laboratory at University College, London, in early August 1884 to discuss the availability of laboratory space for himself, as he was working on the phenomenon of vocal cord paralysis and needed access to the advanced tools held at University College. Whilst conducting experiments on the loss of motor function of the vocal cord, and mostly due to his technical inexperience, Semon experienced

²⁷⁷ The minute book of the Clinical Society documents the meeting in August 1884, where Ord faced the serious possibility of having the Committee discontinued; see Clinical Society of London, "Minute Book of the Clinical Society of London," 317.

²⁷⁸ Letter by Rickman J. Godlee, "Godlee to Clark," August 28, 1884, ClinSoc 16688.1, Royal Society of Medicine.

difficulties in his attempts to electrically stimulate individual nerves.²⁷⁹ One Friday evening, the frustrated Semon asked the only remaining researcher in the laboratory for help. He was astonished to find his experiment running successfully within the hour, although his unsuccessful attempts had taken him the better part of a week.²⁸⁰ The young researcher who came to his aid was Victor Horsley, and he accomplished the task with “technical ability, skill and speed which I have never observed before and rarely since.”²⁸¹ Semon told Horsley about the Clinical Society’s dilemma regarding the myxoedema committee, and the young experimental physiologist was keen to help. Only two weeks later, Horsley had become a member of the Clinical Society and took on the role of scientific medical investigator for the Committee.

Horsley introduced laboratory physiology to the Committee’s repertoire. He had learned from Semon about the Swiss condition associated with the surgical removal of the thyroid gland and was assigned with the surgical investigation of these symptoms by using experimental thyroidectomies in animals. To the Committee’s great benefit, in September 1884, at the age of twenty-seven, Horsley was named Professor-Superintendent at the Brown Animal Sanatory Institute. Schäfer’s laboratory and the Brown Institution were two of the few places in the United Kingdom where animal experiments were permitted, as rules on this kind of experimentation had become quite restrictive after the Cruelty to Animals Act of 1876 and the anti-vivisectionists’ fervour had hardly abated.²⁸² Horsley’s position at the Brown Institution put him in charge of the day-to-day duties, and gave him more freedom of action than at Schäfer’s laboratory. Although he continued to work on his experiments on brain

²⁷⁹ Harrison, *Felix Semon 1849-1921: A Victorian Laryngologist*, 96–97.

²⁸⁰ This experiment was part of the work that resulted in the (now obsolete) law about injury to the recurrent laryngeal nerve, also called Semon’s Law.

²⁸¹ Clinical Society of London, “Minute Book of the Clinical Society of London,” 318.

²⁸² See Richard D. French, *Antivivisection and Medical Science in Victorian Society* (Princeton, N.J.: Princeton University Press, 1975); Nicolaas A. Rupke, “Pro-vivisection in England in the Early 1880s: Arguments and Motives,” in *Vivisection in Historical Perspective*, ed. Nicolaas A. Rupke (London: Croom Helm, 1987), 188–213. For more on the history of the Brown Institution, see G. Wilson, “The Brown Animal Sanatory Insitution,” *Journal of Hygiene* 82 (1979): 155–176, 337–352, 501–521; *ibid.*

localisation, for which he is also well known, he began his work on experimental thyroidectomy about the same time he took up his position at the Brown-Institution on September 21st, 1884.

Initially working with an original member of the Committee, Rickman Godlee, Horsley quickly became the main investigator and removed the thyroid from a wide range of animals, clearly hoping to duplicate the consequences in human patients observed by Kocher and Reverdin in Switzerland. By November 1884, he was able to show to the Pathological Society of London an example of what he called “artificial myxoedema” in a monkey and in December he devoted two of the five Brown Lectures at University College London, which he gave as one of the prerequisites of his position, to the thyroid and its supposed relation to disease.²⁸³ He seemed to support Felix Semon’s hypothesis about thyroid involvement in the pathogenesis of myxoedema explicitly and completely. However, the actual data were a lot less convincing.

Nevertheless, before we come to a discussion of Horsley’s procedures, it will be necessary to contextualise the notion of the thyroid gland’s potential involvement in pathogenetic processes. Over the course of the next two sub-sections of this chapter, I will firstly discuss the medico-scientific context of this idea, and then proceed to an analysis of the difficulties Horsley faced and the results he presented. This will set the stage for a discussion of the Committee’s to find a therapy for myxoedema at the end of the chapter.

As with Kocher’s development of the idea of *cachexia strumipriva*, an identification of the cause of myxoedema related to the thyroid gland was preceded by the organ’s removal and the study of the effects of its absence. Removing the thyroid from its location in the neck had

²⁸³ Horsley, “The Brown Lectures on Pathology.”

only become possible through the general expansion of surgery into the cavity of the body.²⁸⁴

Generally speaking, as we saw in Chapter 1, it was not until the time of Kocher that surgeons were able to remove the thyroid safely even for the treatment of goitres. Subsequently, the removal of the organ became relatively common; although, due to its difficulty and especially the associated risk of *cachexia strumipriva*, it remained a highly disputed procedure.

In the autumn of 1884 Horsley set out to investigate the thyroid's involvement in the pathogenesis of myxoedema, as suggested by Semon. Another incentive was to assess the possibility of therapeutic intervention in what was by then essentially viewed as an incurable condition.²⁸⁵ Comparatively little was known about the thyroid's physiology at the time, but during the 1870s, the idea emerged that this organ was somehow involved in the body's metabolism by way of the central nervous system. Some doctors and medical scientists perceived the organ to act as a "node in the neural matrix of the body."²⁸⁶ One of the dominant concepts in the period of the 1870s and 1880s was the neural theory of the body that the physiologist Eduard Pflüger (1829–1910) of the University of Bonn in Germany had proposed.²⁸⁷ According to Pflüger, the thyroid gland acted as a nexus, through which the central nervous system, the skin, the heart, and the brain were functionally interconnected. As in his theory on the regulation of blood sugar levels, for which Pflüger is probably best known,²⁸⁸ he assumed the existence of an interaction between the organ and the nervous system, and theorised that the proper functioning of the metabolism was regulated by inhibitor and stimulator nerves which were in turn controlled by a spinal reflex centre. To him,

²⁸⁴ Dadan and Nowacka, "A Journey into the Past: The History of Thyroid Surgery"; Owsei Temkin, "The Role of Surgery in the Rise of Modern Medical Thought," *Bulletin of the History of Medicine* 25 (1951): 249.

²⁸⁵ Victor Alexander Hayden Horsley, "On the Function of the Thyroid Gland," *Proceedings of the Royal Society of London* 38 (1885): 5–7.

²⁸⁶ Sengoopta, *The Most Secret Quintessence of Life: Sex, Glands, and Hormones, 1850-1950*, 18.

²⁸⁷ For more details, see: Hans H. Simmer, "Pflüger's Nerve Reflex Theory: The Product of Analogy, Teleology and Neurophysiology," *Clio Medica* 12 (1977): 57–90.

²⁸⁸ As a good example, see his comprehensive overview article: Eduard Pflüger, "Über die im Tierischen Körper sich vollziehende Bildung von Zucker aus Eiweiß und Fett: Zur Lehre vom Diabetes Mellitus," *Pflüger's Archiv für die gesamte Physiologie des Menschen und der Thiere* 103 (1904): 1–66.

this interaction was yet another example of the general principle that governed the self-regulation of life processes. Pflüger's theory was typical for the time in that it used of the nervous system as a key to understanding of all kinds of physiological processes.²⁸⁹

Within this epistemic framework, local damage to the nervous system appeared as a very plausible explanation for the occurrence of a specific set of symptoms following thyroidectomy.²⁹⁰ This was especially the case for an apparently systemic disease, such as myxoedema, with its postulated pathogenetic reliance on the thyroid gland. In order to explain another phenomenon, namely the apparent shrinkage of the thyroid gland, or indeed the inability of physicians to feel the organ during a physical examination—in certain cases of myxoedema,²⁹¹ some scientists postulated that the thyroid's nervous actions should literally be understood as a kind of "secretion." Just as the exocrine glands, like salivary glands, shrank after secretion, so the thyroid would shrink periodically after it had fulfilled its function. The inability to palpate the thyroid gland in cases of myxoedema would consequently amount to the pathologic failure of the thyroid to re-expand, thus leaving it unable to accomplish its neurological function, which in turn would lead to the onset of myxoedematous symptoms.²⁹²

However, such theories remained ambiguous, because they were not based on a convincingly proven function of the thyroid gland. Only by performing animal experiments that combined thyroid removal with a re-grafting of the organ, and thereby enabling the objectifying and controlling effects attributed to the gland, was it possible to construct a clear line of argument. As Horsley later pointed out, it was only this method of constructing an argument

²⁸⁹ For a comprehensive overview see: Edwin Clarke and L. S. Jacyna, *Nineteenth-Century Origins of Neuroscientific Concepts* (London: University of California Press, 1987), chap. 2 & 5. We will encounter Eduard Pflüger again in Chapter 4, where the insistence on his ideas is used as a competing theory to the development of organotherapeutical thyroid replacement therapy.

²⁹⁰ See, for example, Victor Alexander Hayden Horsley, "Further Researches into the Function of the Thyroid Gland and into the Pathological State Produced by Removal of the Same" (1886): 6–9.

²⁹¹ The apparent lack, or severe shrinkage, of the thyroid in cases of the disease has first been observed by Curling in 1850; see Curling, "Two Cases of Absence of the Thyroid Body."

²⁹² Rolleston, *Endocrine Organs*, 99–101.

that could have convinced contemporary medical researchers that the thyroid's function, whatever it may be, was a "scientifically established fact."²⁹³

Clinicians, and especially laryngological surgeons such as Kocher, were thus the first to see whether the neurogenic theory applied to the thyroid gland. At that time, they were the only medical specialists intimately familiar with the physical consequences of total thyroidectomies. Here, it is important to recall the clinical picture proposed for the condition *cachexia strumipriva*, for which the absence of the thyroid gland was presented as a cause, as discussed in Chapter 1. Thus, Kocher argued, the symptoms subsequent to total thyroidectomy could be interpreted as analogous to those of old age, with its decreased mental capabilities, slow movement, etc. Conversely, these surgeons interpreted the effects of neural degeneration as consequences of thyroidal atrophy caused by aging.²⁹⁴ Equating the two phenomena was nevertheless problematic because the dramatic symptoms of organ insufficiency after thyroidectomy were not really comparable to naturally occurring climactic symptoms which varied in intensity and, of course, defied any attempts at 'therapy.'²⁹⁵

3.3. CORRELATING MYXOEDEMA, *CACHEXIA STRUMIPRIVA*, AND SPORADIC CRETINISM: VICTOR HORSLEY'S ANIMAL EXPERIMENTS AND DIAGNOSTIC FIELD WORK

Medical knowledge is advanced by considering observations from the standpoint of pre-existing knowledge. It needs theories to explain and interpret observations. As a result, the next step is to propose an explanation of the observations. This step involves hypothesis formation and theory testing. In this case, the working hypothesis for Horsley was the causal link between the absence of a functional thyroid and the occurrence of myxoedematous

²⁹³ Horsley, "Some Researches Carried Out During the Last Ten Years into the Functions of the Brain and the Thyroid Gland."

²⁹⁴ Bardeleben, "Diskussionsbeitrag zu Kocher's 'Über die Kropfexstirpation und ihre Folgen'," 8; Rudolf Virchow, "Krankheitswesen und Krankheitsursachen," *Virchow's Archiv* 79 (1880): 1–19, 185–228.

²⁹⁵ Robinson, *Endemic Goitre or Thyreocele*, 62.

symptoms. Based on the rigorous clinical observations by the Committee, Horsley then described the problem to be resolved, i.e. the elucidation of the causal account for the occurrence of myxoedema. To his mind, the constant and regular association with the described symptoms supported the proposal of a causal relationship, but required further analysis. The clinicians had applied statistical methods to consider the large set of evidence to determine whether their regular and constant association occurred more frequently than chance would permit. As we have seen in the last chapter, this correlation proved to be problematic. Whilst a common set of symptoms for myxoedema was discernible, the assumed link between excessive amounts of mucin in the body and the occurrence of the disease was highly unlikely. Although the absence of the thyroid gland in cases of myxoedema could not be proven in all cases, and while Semon's questionnaire results failed to provide conclusive evidence, the association of the loss of the thyroid with myxoedema seemed to occur more often than chance seemed to permit. Horsley thus considered it likely, especially given the apparent relation between the surgically induced *cachexia strumipriva* and naturally occurring myxoedema. What resulted was the possibility of an enduring, but dynamic, causal relation, the kind of which will vary in degree of certainty depending on the evidence.

Next to Semon, Horsley became the leading advocate for the link between myxoedema and the thyroid gland on the Committee. By switching fields from surgery to experimental physiology, to neurology and back again,²⁹⁶ he had developed the ability to translate the clinical problem of myxoedema into a form that experimental physiology could deal with.²⁹⁷ Horsley began his thyroid experiments in 1884, not at one of the traditional teaching hospitals in London, but in a university environment that was modelled after Continental laboratories: Sharpey-Schäfer's physiological laboratory at University College. In keeping with the typological differentiation between university and hospital medicine, the non-academic

²⁹⁶ Paget, *Sir Victor Horsley*, 28–29.

²⁹⁷ Borell, "Origins of the Hormone Concept," 58.

teaching hospitals had developed a clinical-pathological approach earlier in the century, but they were not very interested in experimental research and its corresponding scientific approach.²⁹⁸ Horsley, by contrast, belonged to a group of researchers who tried to base medical practice on physiological science. These researchers had all spent time in German laboratories and wanted to establish physiology as an exact and autonomous science in the university context, according to what they had seen in the German-speaking countries.²⁹⁹

In April 1884, Horsley presented a note to the Clinical Society of London summarising his most recent work and outlining the new line of research, which he had been assigned by the Committee's chairman, Ord. This note was the first public statement of his hopes for the elucidation of the cause of myxoedema as well as a probable function of the thyroid gland. The note was titled simply "On the function of the thyroid gland."³⁰⁰ A year earlier, Felix Semon had provoked a rejection by his peers at a similar meeting of the society by suggesting that the loss of the thyroid gland was the causal basis for the development of myxoedema. The difference between Horsley and Semon was that the latter had based his arguments for pursuing this line of enquiry on the publication of the results of Kocher's thyroidectomy experiments. Semon asserted that the thyroid gland played a vital physiological role and that its absence, caused by as yet unknown means, could be the basis of pathological processes, had been directly questioned. Ord had insisted on his own mucin oedema idea, whilst other members questioned the viability of such claims, since all attempts at elucidating the function of the thyroid had either failed or had resulted in speculative conclusions, like Eduard Pflüger's about a potential link to the nervous system, which had not been scientifically proven.

²⁹⁸ For this subject, see Christopher Lawrence, "Incommunicable Knowledge: Science, Technology and the Clinical Art in Britain, 1850-1914," *Journal of Contemporary History* 20 (1985): 503-520.

²⁹⁹ Borell, "Origins of the Hormone Concept," 193-195.

³⁰⁰ Horsley, "On the Function of the Thyroid Gland," 27.

Horsley worked both as a surgeon and as a physiologist, and during his time on the Committee between 1884 and 1888, he was a follower of Eduard Pflüger's notion that there was a link between the thyroid and the central nervous system. Based on Pflüger's assumptions, Horsley expected to see the "pronounced effects of old age," and by extension, the set of symptoms now known as myxoedema. He had planned his experiments "with the conviction to obtain a notable decrease of the powers of action of the nervous system."³⁰¹

Yet, Horsley encountered initial problems with his test animals. At Schäfer's laboratory he had been using cats and dogs for his research on the localisation of brain functions. However, when he attempted to remove the thyroid gland from those animals, he found that they developed tetany and massive spasms, leading to a rapid death between a period of one to five days, whilst the post-mortem examinations revealed nothing.³⁰²

Horsley then procured ten rhesus macaques and seven diana monkeys.³⁰³ Although he never explained the quick death of his canine and feline test subjects, he asserted that primates, due to their closer evolutionary proximity to humans might make for better experimental candidates.³⁰⁴ After total thyroidectomy, these monkeys developed tremors and spasms after a few days, then acquired puffiness of the eyes with a low temperature, listlessness, and hair loss, just as in cases of human myxoedema, and finally died within five to seven weeks. However, more interestingly, the skin of those monkeys at autopsy was swollen and jelly-like, provided the animal had lived at least a month after the operation.³⁰⁵ Horsley had unwittingly caused what we now know as parathyroid deficiency. He concluded that the monkeys had

³⁰¹ Ibid.

³⁰² Ord et al., *Report of a Committee*, 21 (Supplement):68–70.

³⁰³ Ibid., 21 (Supplement):78.

³⁰⁴ Horsley, "Further Researches into the Function of the Thyroid Gland and into the Pathological State Produced by Removal of the Same," 6.

³⁰⁵ Ord et al., *Report of a Committee*, 21 (Supplement):83.

indeed acquired the same disease as human myxoedema; his canine and feline test subjects had simply died too soon to develop it.

These results were, of course, of great interest to Ord, due to the lack of positive results from his clinical sub-committee. Horsley had been brought onto the Committee to investigate the role of the thyroid gland regarding myxoedema. Ord now saw a chance to vindicate his original idea of mucin oedema as the underlying disease mechanism. Given Horsley's experience as both a scientific researcher and a clinician, Ord commissioned Horsley to draw up a first-hand account of cases of myxoedema across the United Kingdom by following up on case reports and offering a second opinion on the correctness of the initial diagnosis. The results of this field work were published by Horsley in 1887.³⁰⁶

At this point, the causal relationship between the symptoms and thyroid removal had only been demonstrated by Kocher's artificially created cases of *cachexia strumipriva* in humans.³⁰⁷ The point was now to show that the same was true for myxoedema, the condition that occurred in adults and children without a previous operation. As we have seen in the first chapter, sporadic cretinism had been recognised on the British Isles since the 1850s. This disease, derived from the endemic form found in Switzerland, provided some of the formative work for what was later named myxoedema. As was the case with endemic cretinism, the sporadic variety had been causally linked to environmental factors, a theory that had been disregarded by Ord in favour of the mucin oedema. Horsley, however, worked from a different angle. Since he was only able to re-create the oedema in monkeys, and the clinical subcommittee failed to find supporting evidence in their case reviews, Horsley took thyroid dysfunction as his working hypothesis. Also, in order to investigate a connection between myxoedema and the earlier case reports published by Curling, Fagge, and Gull between 1850

³⁰⁶ Horsley, "Preventing Cretinism? An Englishman's Perspective."

³⁰⁷ Ibid., 596–601.

and 1873, he tried to correlate sporadic cretinism, *cachexia strumipriva*, and myxoedema. His previous ablation experiments in monkeys had already provided him with a major argument for equating myxoedema and *cachexia*. Since the gradually appearing symptoms Horsley observed were so similar to the myxoedema and cretinism found in human patients, he was convinced that he witnessed the same disease in his laboratory test subjects.³⁰⁸

He began this new line of research with an explicit rejection of the disease entities of cretinism created by his predecessors. He thought that earlier investigators had not recognised the specific clinical picture because they had not known the real cause of the disease. The new definition had to be based on the necessary cause of the disease, which, as Horsley wrote, had to be established as the condition *sine qua non* for the development of genuine sporadic cretinism.³⁰⁹ He counted only those case descriptions in the literature that matched the concept of genuine sporadic cretinism or myxoedema; the remaining cases he classified as other disease entities like deaf-mutism or idiocy. He applied the same strategy in his epidemiological fieldwork. His approach bears a striking resemblance to the research practices of Blackie and McClelland.³¹⁰ Horsley travelled to the south of England and to Lancashire in order to examine cases reports from those regions. He wanted to find out whether sporadic cretinism was also correlated with pathological changes in the thyroid gland, and he examined all of those diagnosed as cretins in the places he visited.³¹¹ In Horsley's opinion, most of the patients presented to him were not cretins at all. Of the thirty diseased people he examined, he accepted only five as cretins; the rest, according to him, were afflicted with different conditions.³¹² The basis of his diagnosis was the similarity of the clinical picture presented to him during his travels with the complex of symptoms that he had

³⁰⁸ Horsley, "The Brown Lectures on Pathology," 212; Ord et al., *Report of a Committee*, 21 (Supplement):78–87.

³⁰⁹ Horsley, "Preventing Cretinism? An Englishman's Perspective," 587.

³¹⁰ These results have been discussed in Chapter 1.

³¹¹ Horsley, "Preventing Cretinism? An Englishman's Perspective," 596–601.

³¹² *Ibid.*, 600.

identified in patients who had undergone total thyroidectomies, as well as in his laboratory monkeys. In other words, he was on the lookout for similarities to Kocher's *cachexia strumipriva* and artificially induced myxoedema. This approach was of course very different from that of his predecessors. As a next step, Horsley examined the thyroids of the five foregoing cretins and found that three of them had goitre, while the other two appeared to have no thyroid at all. To Horsley, this discovery confirmed that sporadic cretinism, like Kocher's *cachexia strumipriva*, was indeed caused by a lack of thyroid function. To his mind, he had thus identified the necessary cause of cretinism, but his findings applied only to cases of cretinism caused by a lack of thyroid function. In other words, he made *genuine* cretinism symptomatically identical to myxoedema as well as postoperative *cachexia*. However, this meant that cretinism could from now on only be classed as *genuine* when it was caused by thyroid insufficiency.

When it came to individual diagnosis, however, Horsley was much more confident than his predecessors. "We have now reached the point, where we can differentiate immediately between a cretin and a patient with another illness, a deaf-mute, a mentally deficient person, or any other kind of idiocy, and where every medical student can make the diagnosis with certainty."³¹³ He based this newly acquired certainty on the knowledge of the necessary cause: "We now know that the pathological disorder concerns a certain organ, that the affliction of this and only this organ is the cause for the development of genuine cretinism. We can formulate this claim as follows: *we now know the cause of cretinism*, inasmuch as one can speak of a cause when one is able to determine the pathological and anatomical basis of an illness."³¹⁴ The main focus was now on the disease's direct cause that must be located inside the body. Moreover, as Horsley at the end of his paper remarked, concentrating on a single cause contrasted with the pre-1883 accumulation of partial causes: "Instead of a large

³¹³ Ibid., 606.

³¹⁴ Ibid., 610–611. Emphasis in original.

number of interacting causes in combination, to induce such shocking decline in human beings, it turned out that the failure of a very small gland, hitherto considered insignificant, was able to bring about the clinical picture of cretinism within a few years, even months.”³¹⁵

Thus, in contrast to his predecessors who constructed their disease entity on the basis of symptoms in order to find out their causes afterwards, it was Horsley’s explicit aim to start out from the disease’s cause and then describe the symptoms. Nonetheless, much like the earlier work on endemic cretinism, Horsley did not discover a naturally occurring disease entity but he constructed one according to the new concept. The “old” cretinism and the “new” myxoedema were therefore not identical. The older endemic disease entity did not have organ failure as its necessary cause; this was only true for the new sporadic cretinism, myxoedema, and *cachexia strumipriva*, whose construction was based on organ failure. Horsley’s redefinition of the disease entities for these conditions and of thyroid deficiency disease in general serves as just one example of the fact that when doctors and scientists began to attribute necessary causes to diseases, they actually had to redefine those diseases.³¹⁶ This redefinition, at least for Horsley, led to the correlation of (sporadic) cretinism, myxoedema, and *cachexia strumipriva* into one clinical entity, which he, in an attempt at unification and in accordance with his work for the Committee, generally referred to as myxoedema.³¹⁷

3.4. THE (IM-)POSSIBLE PATH TO THERAPY

The redefinition and unification of previously separate diseases into one overarching disease entity led Horsley to pursue an additional goal: the attempt to develop a course of treatment. As we saw in the last chapter, the clinical sub-committee stuck to the common practice of

³¹⁵ Ibid., 625.

³¹⁶ For this connection between etiological characterisation and necessary cause of disease, see also: Carter, “Ignaz Semmelweis, Carl Mayrhofer, and the Rise of Germ Theory,” 33–34.

³¹⁷ Ord et al., *Report of a Committee*, 21 (Supplement):199.

recommending stimulants as a therapeutic approach in cases of myxoedema. However, based on his own conclusions, Horsley aimed at a more radical approach, one that was based on his assumption of the thyroid being the causal link in the disease. If the data he reviewed painted a clear picture, and if his conclusions based on his laboratory and clinical field research were to be believed, the most rational way to approach the matter of treatment for a disease that resulted from the deficiency of the thyroid gland would be to surgically replace that organ.

Horsley began to develop these ideas in late 1887 when Ord was already in the process of wrapping up the results of the Committee for the final report. Horsley's proposal for surgical thyroid replacement was too speculative and too ambitious to be ascertained in the space of a few months for it to be considered for inclusion in the final report. Instead, Horsley took the results from his 1887 paper and drafted a brief article that called for further investigations into experimental thyroid transplantations as a possible means to counteract the effects of chronic thyroid dysfunction.³¹⁸

From 1888 to 1891, Horsley conducted experiments that initially seemed promising. In the years of his extirpation and transplantation experiments on animals, Horsley had systematically continued his endeavours, which he based by and large on the work he had carried during his time on the committee, i.e. with thyroid extirpations in monkeys; but this time, he attempted to reverse the process. He had almost stubbornly held on to the development of thyroid transplantation despite the change of opinion from his peers.³¹⁹ According to Theodor Kocher, he was "the most zealous and consequential researcher" in the

³¹⁸ Victor Alexander Hayden Horsley, "Note on a Possible Means of Arresting the Progress of Myxoedema, Cachexia Strumipriva, and Allied Diseases," *British Medical Journal* 1 (1887): 287–288.

³¹⁹ For example, see Horsley, "Some Researches Carried Out During the Last Ten Years into the Functions of the Brain and the Thyroid Gland"; Sigfrid Knauer, "Organtransplantationen," in *Die Freien Transplantationen*, ed. Erich Lexer, vol. 1 (Stuttgart: Enke, 1912), 33–43; Bornhauser, *Zur Geschichte der Schilddrüsen- und Kropfforschung im 19. Jahrhundert (unter besonderer Berücksichtigung der Schweiz)*, 148; Paget, *Sir Victor Horsley*, 69.

field.³²⁰ In contrast to most other researchers, Horsley was convinced that, after successful implantation of a new thyroid in the recipient's body, the transplant would regenerate, acquire a new blood supply, and exercise its function as a replacement proper.

Horsley defined some conditions for the success of possible thyroid transplantability. Firstly, he held that the tissue should be grafted into the recipients' organism in the form of small, multiple samples. And secondly, he stated that transplantation across species seemed to be highly questionable. However, in his own experiments, Horsley completely ignored the issue of autogenous and allogenic grafting, i.e. whether the thyroid gland transplanted in his experiments was the one of the monkey itself, grafted into another location, or whether it originated from another monkey of the same species. His results indicate that he presented the results of autogenous grafting as evidence for the possibility of successful transplantation within the same species.³²¹

In 1890, Horsley reported a series of experimental transplantations in which he set out to test several combinations of functional and atrophied thyroid tissue in both initially healthy as well as previously thyroidectomised rhesus macaques. In each case, he subsequently removed the grafts and examined the results by histological analysis.³²² He found that generally the healthier the tissue employed for the operation, the better the outcome tended to be. When thinking about the potential clinical application of his idea, Horsley conceded that healthy human thyroid tissue would be hard to acquire; thus, he recommended the use of human thyroid glands exhibiting the signs of goitre, but only as long as the organ showed only slight

³²⁰ Kocher, "Über die Bedingungen erfolgreicher Schilddrüsenimplantation beim Menschen," 499. Similar assessments can be found in Ernest W. Hey Groves and Cecil Joll, "Thyroid Grafting and Surgical Treatment of Exophthalmic Goitre," *British Medical Journal* 2 (1910): 1966; Knauer, "Organtransplantationen," 33.

³²¹ This has also been noticed by Woodruff, see: Woodruff, *The Transplantation of Tissues and Organs*, 485–487.

³²² Victor Alexander Hayden Horsley, "Experimental Transplantation of the Thyroid in Rhesus Macaques, Containing a Histological Analysis," *Transactions of the Pathological Society of London* 41 (1890): 212–215.

pathological changes. As the final important factor for a successful outcome, he identified the recipient's requirement for thyroid function. However, this should not outweigh the physiological stress put on the grafts, so as not to destroy the new tissue from overuse.³²³

Horsley reported the results of a very successful investigation later the same year. In this case, he had operated on the receiving monkey several times after the initial transplantation to identify the healing stages of the graft.³²⁴ The monkey first underwent a total thyroidectomy and was left in that state for five weeks for myxoedematous symptoms to develop. The preserved thyroid was cut into small chunks and grafted under the skin of the monkey's throat. Horsley identified three healing stages: resorption, vascularisation, and maintenance.

The initial phase of resorption of parts of the thyroid tissue brought about an immediate and striking effect, which was followed by vascularisation that seemed to vary in length, depending on the size of the grafted tissue sample. With the smallest pieces of thyroid tissue, Horsley observed that the final stage of maintenance began after about six weeks. Horsley argued that during this final phase the surviving pieces of organ tissue began to function like their original counterpart. Based on this outcome, Horsley evaluated this series of experiments as successful. The monkeys looked better, acted normal, and needed far less care than during the myxoedematous condition after thyroidectomy. In order to gain even better results, Horsley operated on one monkey again after a period of four months. On this occasion, he increased the amount of thyroid tissue, which he extracted from another monkey, for grafting by two, and divided the organ into twenty-six pieces. After this second operation, the monkey was judged as having completely recovered from the effects of the thyroidectomy. To Horsley, this was "undisputable evidence," not only that thyroid transplantation was effectively possible, but also that the grafts could survive. He conjectured

³²³ Ibid., 215.

³²⁴ Victor Alexander Hayden Horsley, "Functional Hypertrophy of Grafted Thyroid Tissues," *Transactions of the Pathological Society of London* 42 (1890): 116–122.

that the treatment would be just as possible in human patients as it was in his laboratory animals.³²⁵

By 1890, a whole series of reports of experimental thyroid transplantations were published. Many of these accounts came from the United Kingdom, but some also originated in France, Portugal and Germany. The usual test subjects were sheep and monkeys, and the thyroids used for transplantation exclusively came from sheep.³²⁶ Most authors observed a positive effect on their laboratory animals but usually saw themselves in no position to decide whether the results stemmed from the resorption of the thyroid tissue or were due to a genuine survival and functioning of the transplanted organ.

In 1890, Anton von Eiselsberg (1860–1939) at the University of Vienna reported the transplant of feline thyroids.³²⁷ He even went as far as to attempt the operation on a fifty-four-year-old woman to treat “a case of tetany” after the near-total extirpation of a cancerous goitre, and grafted a small piece of a sheep’s freshly extracted hypertrophic thyroid into her abdominal wall.³²⁸ He used exactly the same technique he had used on his cats. The operation was, however, not successful and the patient died of tetany. During the subsequent autopsy, von Eiselsberg found the transplanted tissue necrotic and surrounded by pus. He attributed this

³²⁵ Ibid., 122.

³²⁶ A. M. Bettencourt and J. A. Serrano, “Un Cas de Myxoedème Traité par la greffe hypodermique du corps thyroïd d’un mouton,” *La Semaine Médicale* 10 (1890): 294; British Medical Journal, “Thyroid Grafting” 2 (1887): 590; British Medical Journal, “Note on the Transplantability of the Thyroid Gland,” *British Medical Journal* 1 (1888): 1490; Merklen, “Sur un cas de myxo amélioré par la greffe thyroïdienne,” *La Semaine Médicale* 10 (1890): 426; Odilon Marc Lannelongue, “Transplantation du Corps Thyroïde,” *Le Bulletin Médical* 4 (1889): 225. The application by the thyroid surgery specialist Anton Wölfler represented a variation. He transplanted a piece of lamb thyroid prophylactically into the neck of a monkey before extirpating the recipient’s gland. Wölfler had, in any case, also left some original thyroid behind; see: Eugen Enderlen, “Untersuchungen über die Transplantation der Schilddrüse in die Bauchhöhle von Katzen und Hunden,” *Mitteilungen aus den Grenzgebieten der Medizin und Chirurgie* 3 (1898): 524.

³²⁷ Anton Freiherr von Eiselsberg, “Über erfolgreiche Einheilung der Katzenschilddrüse in die Bauchdecke und Auftreten von Tetanie nach deren Exstirpation,” *Wiener Klinische Wochenschrift* 5 (1890): 81–85.

³²⁸ Anton Freiherr von Eiselsberg, “Zur Frage der dauernden Einheilung verpflanzter Schilddrüsen, zugleich ein Beitrag zur postoperativen Tetania,” *Verhandlungen der Deutschen Gesellschaft für Chirurgie* 43 (1890): 655–669.

failure to a breach of asepsis and to the poor state of the transplanted pieces of the organ; but he never mentioned or considered the fact that in his experiment on cats, he used transplants from the same species, whilst in his human patient, he had used ovine thyroid tissue.

The very same year, John Macpherson in Edinburgh published a paper on a subcutaneous thyroid transplantation from a live sheep. He attributed the immediate, observable effects on a thyroidectomised monkey to the resorption of the transferred tissue, but assumed that a large part of the tissue he had grafted had taken well in the animal's body. In his opinion, the transplantation of the thyroid gland was far superior to the merely palliative, and uncertain, treatment by stimulants.³²⁹ Around the same time, a Lyonnais experimenter by the name of V. Robin reported on the initially successful experiment in a monkey with jaborandi. As pronounced side effects occurred, particularly abscesses, Robin changed his approach and performed a subcutaneous transplant of a thyroid gland from a sheep. He reported good results and emphasised that treating a potential patient regularly with jaborandi in addition to the operation would increase the graft's chances of success.³³⁰

One of the factors considered to be important for a successful thyroid transplant was the site of implantation. Thyroid tissue could be grafted directly under the skin (subcutaneously), within a muscle (intramuscularly), in front of the peritoneum (properitoneally), into the abdominal cavity itself, or into the greater omentum.³³¹ Theodor Kocher had observed that thyroid tumour cells had a tendency to colonise the cavities of bones as well, which made their medullary cavity a potential grafting site, as well.³³² In search of a potential grafting site with access to a good supply of blood, the Glasgow physiologist Eugene Huskins tried out the

³²⁹ John Macpherson, "Notes on Experimental Thyroid Grafting," *Edinburgh Medical Journal* 35 (1890): 1021–1024.

³³⁰ V. Robin, "Myxoedème traité par le greffe des corps thyroïde des moutons," *Gazette Hebdomadaire de Médecine et de Chirurgie* 27 (1890): 451–453.

³³¹ Knauer, "Organtransplantationen," 86–88.

³³² Theodor E. Kocher, "Die Pathologie der Schilddrüse. Zweites Referat," in *Verhandlungen des Congresses für Innere Medizin*, vol. 9 (Wiesbaden: Bergmann, 1890), 68.

well-supplied spleen. His goal, he asserted, was to provide an organism without thyroid or thyroidal function a replacement that would be capable of surviving and functioning for a long time, potentially for good.³³³ In animal experiments, he developed a technique that consisted of slicing the thyroid and inserting the slices into a prepared pocket inside the spleen, which he then sealed with parts of the greater omentum.³³⁴ In December 1890, Huskins used the procedure in its entirety on a dog whose thyroid gland he had extirpated shortly before the procedure. Initially, he observed none of the tetanic convulsions reported by Horsley and others; long-term improvement, however, fell far short of his expectations, as the dog died within two weeks after the operation, exhibiting all the well-known drastic symptoms of thyroid removal in canines. Huskins experienced the negative outcome as a major set-back and vowed to distain from similar experiments in the future. However, as late as 1912 he still claimed that the spleen would, at least in principle, be the optimal site for thyroid grafts.³³⁵

In 1891, the *British Medical Journal* published a brief summary of the state of thyroid gland transplantation, which included a report on an apparently successful transplant: following Victor Horsley's personal advice, two young researchers at University College, London, grafted thyroid tissue into a dog, with good results.³³⁶ The same year, however, Horsley published another report on his research and came to a much less favourable conclusion. Having reviewed the literature and taking into account his own experiments, he conceded that only about one quarter of all experimental case studies were successful and, as he himself admitted, even these successes were quite debatable, especially regarding their long term viability.³³⁷

³³³ Eugene Huskins, "Transplantation of Thyroid Tissue," *Glasgow Medical Journal* 7 (1891): 28–35.

³³⁴ *Ibid.*, 30.

³³⁵ Eugene Huskins, "On the Question of Thyroid Transplantation," *The Lancet* 2 (1912): 987–988.

³³⁶ British Medical Journal, "Thyroid Grafting in Britain," *British Medical Journal* 1 (1891): 216.

³³⁷ Victor Alexander Hayden Horsley, "On the Conditions of Thyroid Transplantation," *Transactions of the Clinical Society of London* 24 (1891): 212–216. For the problems of assessing success in this area, see Chapter 6 of this thesis.

By 1891, then, most researchers seem to have become rather sceptical about the viability of thyroid grafting, especially as a potential therapeutic measure. Theodor Kocher wrote that the profession should not keep up its hopes for the success of this method.³³⁸ The general assumption was that the grafted thyroid gland would eventually perish³³⁹ and that the method was not suitable for clinical practice.³⁴⁰ The scepticism was no longer just about whether transplants of the thyroid were viable, but whether they could be made to have a lasting effect. Far too many reports on failures and doubts in this respect had appeared, and the literature on animal experiments indicated that lasting success and long-term survival could not be expected any time soon.³⁴¹

3.5. CONCLUSIONS OF THE FINAL REPORT OF THE MYXOEDEMA COMMITTEE

Ord, writing for the Committee, summarised the evidence in the final conclusions of the report in 1888. He stated that myxoedema was a “distinctly marked and defined disease [...] and in a few cases [it] has been preceded by exophthalmic goitre.”³⁴² Ord felt that Semon “might have exhibited good judgement”³⁴³ in pointing out the possible connection between myxoedema and the thyroid gland, but noted that clinical and scientific proof of this assumption were still pending. As to treatment nothing further was proposed; only warmth, jaborandi or pilocarpine, and nitro-glycerine were mentioned as favourable.³⁴⁴ Horsley’s proposal to treat the condition with thyroid grafting was not mentioned.

³³⁸ Theodor E. Kocher, “Ein Fall von Kachexia mit Struma,” *Correspondenzblatt für Schweizer Ärzte* 21 (1891): 143.

³³⁹ P. Watson Williams, “Notes on Myxoedema Treated with Extract and Graft of Sheep’s Thyroid,” *British Medical Journal* 2 (1894): 1303–1304.

³⁴⁰ Bornhauser, *Zur Geschichte der Schilddrüsen- und Kropfforschung im 19. Jahrhundert (unter besonderer Berücksichtigung der Schweiz)*, 68.

³⁴¹ Woodruff, *The Transplantation of Tissues and Organs*, 485.

³⁴² Ord et al., *Report of a Committee*, 21 (Supplement):177.

³⁴³ *Ibid.*, 21 (Supplement):196.

³⁴⁴ *Ibid.*, 21 (Supplement):185.

As to the questions of why no mucin oedemas occurred in most human patients, and why the clinical syndrome did not exactly match the experimentally induced one, and why less than half of the patients who had undergone a thyroidectomy developed myxoedematous symptoms, Ord opted for qualifications in his conclusions. He chose to consider the phenomenon of excessive mucin only a stage in the disease process that one could pass through. He glossed over the differences between the clinical syndrome he had himself described in 1878 and that seen by Horsley in the thyroidectomised monkeys. He also chose to look favourably on the one-third of thyroidectomised patients who developed myxoedema rather than on the two-thirds who did not.

The fifteen brief conclusions provided at the end of the report were a lot more decisive than the actual evidence produced over the five years the Committee sat might have suggested. However, all members adopted them unanimously.³⁴⁵ The second to last conclusion was a nod of approval towards Horsley's ideas: "14. [A] general review of symptoms and pathology leads to the belief that myxoedema, as observed in adults, is practically the same disease as that named sporadic cretinism; that myxoedema is probably identical with cachexia strumipriva; and that a very close affinity exists between myxoedema and endemic cretinism."³⁴⁶ However, the final point made the proviso that: "15. While these [diseases] depend on, or are associated with, destruction or loss of the thyroid gland, the ultimate cause of such destruction or loss is at present not evident."³⁴⁷

The Clinical Society of London supported the Report financially as well as scientifically. Its annual report for 1886 noted that they expected the final account to be published in 1887. However, publication had to be delayed until May 1888, due to financial difficulties. The

³⁴⁵ As evidenced by the signatures of all committee members at the end of the overall conclusions. *Ibid.*, 21 (Supplement):202.

³⁴⁶ *Ibid.*

³⁴⁷ *Ibid.*

society had to accept a donation of £100 from William Ord in order to defray the printing costs, or would have faced bankruptcy. It was hoped to recoup some of the overall £400 cost by selling a portion of the 1350 printed copies.³⁴⁸

The Report was avidly awaited, too. Advance notice of its publication appeared in the *British Medical Journal* one week before the official launch on May 25, 1888, and it was reported as far away as Cincinnati, Ohio. The fifteen conclusions rapidly appeared, not surprisingly, in the Clinical Society's own *Transactions* as well as in the *British Medical Journal*. Within two months, the conclusions were reprinted in New York and Philadelphia as well. The uncertainties of the actual data were not disseminated, however; the reporting correspondents judged that the readers were mainly interested in the crystallised conclusions.

The final question we have to address in relation to the *Report* and the research carried out by Horsley and others in an attempt to go beyond the tentative characterisation of myxoedema by the Committee, is how the themes of clinical observation, discussed in the last chapter, and their scientific explanation contributed to an understanding of myxoedema. As we have seen, clinical observation alone was insufficient to generate a deeper understanding of the disease, or even to go beyond the existing knowledge. A theory based on physiological knowledge, gained from experimental investigations, was also needed to scientifically explain the clinical observations for them to lead to the desired understanding. Horsley's monkey experiments for the Committee were such attempts at scientific explanation. In turn, in order to elevate the experimental results to the status of theory, they needed to be interpreted in light of clinical or physiological knowledge. However, it became apparent that the existing knowledge could not explain the phenomenon in question. Horsley responded to this

³⁴⁸ Clinical Society of London, "Report of the Council of the Clinical Society," *Transactions of the Clinical Society of London* 20 (1887): lx; *ibid.*; *ibid.*

challenge by investigating whether his fellow researchers could report similar observations of the decrease of myxoedematous symptoms after thyroid grafting. He took the statistical correlation as an indication of the existence of a causal process, and that the processes assumed by Ord in 1878 were probably not contributing to the occurrence of myxoedema. The apparent weakness of Horsley's association means that his explanation was at best temporal, but it was not merely arbitrary. His account freed the research into myxoedema from the contradictions and *ad hoc* assumptions that had resulted from the clinical observations based on Ord's ideas.

This brings us full circle with the problems faced by the clinicians on the Committee. We have seen that when a reliable explanation, i.e. one that can be replicated by other investigators, is at present not possible, the conclusions drawn can only play a limited role in medicine's understanding of the disease. The same happened to Horsley's thyroid experiments as an attempt at scientific explanation. Although these were carried out with all the scientific rigour necessary, their reproducibility proved inconclusive. However, the aim of the *Report* had never been to lead to final and complete truths about myxoedema. Rather, the results were by necessity open-ended and open to change. Open-ended observations and explanations were not necessarily false, poorly supported, or not worth paying attention to. These types of explanations have actually far greater intellectual weight and authority than proposed explanations that have not been subjected to the requirements of proper medical investigation. Thus, the understanding of myxoedema may, at this point, have been incomplete, but it was not relative, because the scientific explanation was not arbitrary.

3.6. CONCLUSION

We are now left with the question, whether the proposal of Horsley's, and by extension Semon's, of a causal link between the thyroid gland and the redefined myxoedema, i.e. a unification between myxoedema/*cachexia strumipriva*/(sporadic) cretinism, was viable. The

excursion into thyroid transplantation experiments has been judged as a failure by recent historiography, especially by Thomas Schlich and David Hamilton.³⁴⁹ However, this perceived failure is one in the context of the development of the technique of therapeutic transplantations only. What concerns us here, is the association of the organ with an underlying disease entity. And in this respect, the results obtained are not an outright disappointment. In the cases of experiments in which the grafts had taken to the recipient's body, the associated symptoms of thyroid deficiency had, after all, been alleviated. The problem, thus, did not so much seem to be one of a problematic connection, but one of technical, i.e. surgical, difficulty. Consequently, Schlich and Hamilton's assessment does make sense in retrospective analysis of a novel surgical procedure, i.e. the development of therapeutic organ transplantation. However, in the context of the present thesis, and taking into account the methodological framework employed, the techniques used, results gained and conclusions drawn by Horsley and his peers fall squarely into what John Pickstone has called the second way of knowing, i.e. analysis. In the next chapter, this theme will be taken further by discussing the initial assumption of a connection between thyroid failure, or its absence, as the basis for an approach that was technically far less difficult. Here, the replacement of the gland was attempted not by means of surgical intervention, but by the experimental investigation of the hypothesis of an active constituent of the thyroid, which could replace the assumed function of the gland. The results, as we will see, are far less problematic.

This chapter has shown that an assessment of the results of the Committee's *Report* may not be straightforward, but certainly does not condemn it to the status of an outright failure. The examination of the development of a pathological concept for the thyroid and the subsequent redefinition of the previously distinct clinical entities of myxoedema, *cachexia strumipriva*,

³⁴⁹ Schlich, *The Origins of Organ Transplantation: Surgery and Laboratory Science, 1880-1930*, 54–56; Hamilton, *A History of Organ Transplantation: Ancient Legends to Modern Medicine*, 77, 97–98.

and cretinism into one unified entity, has shown that the causal association of myxoedema and the loss of the thyroid gland was a viable research hypothesis, although certainly a tentative one.

In considering how myxoedema has changed over the course of attempts at its scientific analysis, this chapter, in conjunction with Chapter 2, links to the developments described in the following chapter, i.e., following through with Pickstone's three ways of knowing, experimentation. The, albeit tentative, scientific exploration of thyroid gland pathology and the link to myxoedema opened up this field of medical research for further experimental investigations which would lead not only to the proof of Horsley's and Semon's assertion, but also to the cure of the previously untreatable disease, myxoedema, by way of thyroid gland replacement therapy.

– CHAPTER 4 –

EXPERIMENTATION: ORGANOOTHERAPY AND THE TREATMENT OF MYXOEDEMA

4.1. INTRODUCTION

It was not solely the results published in the *Report* of the committee of the Clinical Society of London that demonstrated the importance of research on myxoedema to doctors and scientists at the end of the nineteenth century. This chapter investigates the researches performed at the intersection of the clinic and laboratory, including everyday medical practice from the standpoint of Pickstone's third way of knowing: experimentation, i.e. the testing with the results relevant to the truth or falsity of the hypothesis of a causal link between the thyroid gland and the occurrence of myxoedema. This is particularly important because, as has been discussed over the course of the first and second chapter of the thesis, prior to myxoedema's causal attribution to the function of the thyroid gland, this condition was as much a mystery as any other loosely defined syndrome. Prior to the published Committee *Report* of 1888, the disease entity of myxoedema was based on its supposed main symptom, the accumulation of mucin in the lower layers of the patient's skin. After the *Report*, the consensus was that myxoedema should be symptomatically characterised by dropsy, hair loss, physical weakness, and diminished mental capabilities. The characterisation thus followed the clinical picture and not a causal mechanism. In his 1890 article, William Ord summarised the state of the art of research on this mechanism: to that date, neither clinical classification nor pathological anatomy or physiological chemistry had revealed the cause and pathogenesis of myxoedema, and pathologists had not been able to associate the condition with any

identifiable lesion of a particular organ beyond reasonable doubt.³⁵⁰ None of the numerous localisations deemed, at least in principle, possible seemed convincing.

Since the rising interest in cretinism and goitre in Britain, findings of pathological changes in the thyroid had sporadically given rise to speculations about the contribution of that organ to the pathomechanisms of these diseases and, by extension, to myxoedema during the 1880s. However, due to the prevailing ignorance regarding its physiological function, thyroid gland involvement seemed no better or worse an option than attempting to frame myxoedema as a skin disease or as a special form of Addison's disease resulting from kidney dysfunction.³⁵¹ None of these findings, despite the *Report* favouring possible thyroidal involvement, led to the redefinition of myxoedema as an organ disease. Instead, the new definition was brought about by experimental clinical research after 1891. Thus, following through with Pickstone's *Ways of Knowing*, this chapter brings the narrative about the genesis of myxoedema as an organ based disease with a clear causal attribution full circle. The natural history approach of the first and second chapter enabled the analysis of the catalogued and classified phenomena relating to sporadic cretinism and the physiology of the thyroid gland enabled their scientific analysis, as discussed in the third chapter. In tandem, these two ways of knowing enabled experimentation and synthesis, the third way of knowing, allowing control of the conditions for the production of novel phenomena and products, i.e. thyroid replacement therapy as a cure for myxoedema.

This first part of this chapter focuses on the development of the concept of organotherapy in France, which, in turn, was based on the physiological notion of *internal secretion*. This concept was of particular importance as it provided a usable framework for the clinical

³⁵⁰ Ord, "The Present State of Myxoedema: Being a Discussion of the Relevant Clinical Signs of the Disease." However, as was the case in his overall conclusion to the Report on Myxoedema, Ord suggested that the thyroid gland was a promising contender.

³⁵¹ Lancaster, "Notes and Reflections on the Thyroid and Its Relation to Disease."

application of the laboratory based results discussed in the preceding chapters. The largely sceptical reception of the French ideas by the British medical community forms the subject of the second section. The five subsequent sections of this chapter analyse the development of the therapeutic turning point for myxoedema based on the use of medically active preparations of liquefied thyroid glands. This therapy, which was perceived by many as the ultimate proof of the causal link between thyroid dysfunction and the onset of myxoedematous symptoms, was soon framed as a “rational” therapy.

4.2. THE CONCEPT OF ORGANOTHERAPY

Performing experimental research on either the thyroid or myxoedema was not a new idea at that time. As discussed in the preceding chapter, the work of Victor Horsley, carried out between 1884 and 1887, for the Committee was of this kind, and some findings of the report itself were based on his results from experimental physiology. In addition, experimental thyroid studies had been performed since the early nineteenth century in Britain and during the 1850s, Moritz Schiff showed that the removal of the thyroid gland in dogs had devastating effects on the animals.³⁵²

Despite these attempts, experimental physiologists had been unable to narrow down the cause of the disease, let alone control it. They were not able to induce or eliminate myxoedematous symptoms arbitrarily and the British physiologist Michael Foster (1836–1907) assumed in 1881 that the condition might stem from a variety of sources, depending on the individual’s case.³⁵³ As a result, no reliable course of treatment was available, and myxoedema remained a disease with an ultimately fatal course. All the supposed therapies

³⁵² See Chapter 1 for a discussion of those experiments.

³⁵³ Michael Foster, *Pathological Physiology* (London: Murray, 1881), 211.

eventually turned out to be useless, and physicians lost hope in the pharmaceutical treatability of the condition.³⁵⁴

Help arrived from an unexpected quarter. By the early 1890s, the study of internal secretions had become a research topic among physiologists, predominantly in France. The idea had originated with the French experimental physiologist Claude Bernard (1813–1878), who had first proposed the concept in 1853 in order to differentiate between two processes: the secretion of bile from the liver into the intestines (an *external* secretion), and the release of glucose from the liver into the blood stream (an *internal* secretion).³⁵⁵ However, it took nearly three decades for the concept to become an applicable therapeutic programme. This programme became known as ‘organotherapy’ and began to draw the attention of medical scientists toward internal secretion.³⁵⁶

The concept of organotherapy had originated two years earlier in studies on rejuvenation conducted by the French experimental physiologist and neurologist Charles Eduard Brown-Séquard (1817–1894) and his assistant Jacques-Arsène d’Arsonval (1851–1940). At a meeting of the Society of Biology in Paris in 1889, Brown-Séquard had argued that the mental feebleness characteristic of men was a result of reduced testicular function. The testicles, he

³⁵⁴ Ibid.

³⁵⁵ Claude Bernard, *Leçons sur les propriétés physiologiques et les altérations pathologiques des liquides de l’organisme*, vol. 2 (Paris: J.B. Baillière, 1855), 490–492.

Bernard has often been presented as the originator of the theory behind the organ replacement concept; e.g. see: Rolleston, *Endocrine Organs*, 133–134; Borell, “Origins of the Hormone Concept,” 28; Schlich, *The Origins of Organ Transplantation: Surgery and Laboratory Science, 1880-1930*, 55. However, this designation is misleading. Primarily, because thirty years intervened between the introduction of the term “internal secretion” and its popularisation by Brown-Séquard in his therapeutic programme.

To my knowledge, the historian of chemistry F.G. Young was the only one to argue, based on his reading of Bernard’s lectures, that Claude Bernard extended the concept to the products of the blood glands (spleen, thyroid, and supra-renal glands); see: F G Young, “The Evolution of Ideas About Animal Hormones,” in *The Chemistry of Life: Eight Lectures on the History of Biochemistry*, ed. Joseph Needham (Cambridge: Cambridge University Press, 1971), 127.

³⁵⁶ This section is only a brief summary of the development and meaning of the concept of organotherapy. Merriley Elaine Borell’s 1976 PhD thesis provides a much more detailed and nuanced discussion of this topic and its reception; see: Borell, “Origins of the Hormone Concept,” chap. 1 & 2.

continued, probably produced a “dynamogenic” substance that might be extracted from the testes of animals and injected into aging or debilitating individuals to restore their strength.³⁵⁷ For this aim, Brown-Séquard rested his argument on commonly held assumptions about the link between human sexuality and general health. For example, it was widely held that loss of semen resulted in the loss of strength, and that the practice of masturbation would lead to debility.³⁵⁸ He argued that retention or restoration of semen ought to increase strength and vigour. He suggested further that the testes produced some substance, an *internal* secretion, which was nutritive to the nerves, and which might be extracted and used to such effect.³⁵⁹ These ideas attracted the attention of both professionals and laypersons; and legitimate doctors, medical scientists, as well as all manner of quacks, began to emulate him. In order to disseminate his method, Brown-Séquard sent out extract from his Parisian laboratory free of charge if the recipients would reciprocate by reporting their experiences with it. At the end of 1889, the extract was being evaluated all over the world by nearly twelve thousand individuals, and within a very short time, testicular fluid was being used as a remedy for all kinds of diseases.³⁶⁰

Initially, Brown-Séquard and d’Arsonval applied organotherapy only to the testes; subsequently, however, Brown-Séquard attributed some type of internal secretion to all organs and tissues of the body. By April 1890 the duo was testing extracts of the pancreas for

³⁵⁷ Charles-Éduard Brown-Séquard, “Des effets produits chez l’homme par des injections sous-cutanées d’un liquid retire des testicules de cobaye et de chien,” *Comptes rendus de Société de Biologie* 1 (1889): 415–419.

³⁵⁸ Thomas Walter Lacquer, *Solitary Sex: A Cultural History of Masturbation* (New York: Zone Books, 2003), 86.

³⁵⁹ Brown-Séquard, “Des effets produits chez l’homme par des injections sous-cutanées d’un liquid retire des testicules de cobaye et de chien.”

³⁶⁰ Borell, “Origins of the Hormone Concept,” 18–25.

diabetes; of the spleen for intermittent fever; of the thyroid and bone marrow for anaemia; of the adrenal cortex for Addison's disease; and of muscles for muscular weakness.³⁶¹

But not everyone was enthusiastic about organotherapy. To many scientifically oriented doctors, the method reeked of charlatanism. William Ord stated in 1890 that one would "just expect [to] find a proposal of this kind in a quack's handbook instead of the therapeutic arsenal of modern medicine."³⁶² One of the major shortcomings of organotherapy was that it deviated vastly from the scientific ideals of medicine at the time, mainly because it did not aim to control a single crucial factor in the pathological process but promised an unspecific, generally tonic effect. It was used to treat diseases that were not defined clearly, and certainly not in terms of a necessary cause. Thus Brown-Séquard's method ultimately made it almost impossible to evaluate any therapeutic outcomes.

The rationale for the introduction of organotherapy into medicine was developed largely in France, but much of the evidence for the validity of its claims and its relevance for clinical practice came from the work of British physicians as we will see in the following sections. Important discoveries were made in Britain in the early 1890s, which added credence to the notion of internal secretion. One of these discoveries was the cure of myxoedema by subcutaneous injection of liquefied thyroid glands, as reported in 1891 by George Redmayne Murray of Durham University's medical school at Newcastle-upon-Tyne.³⁶³ This discovery effectively transformed the research programme by designating an alternative to the essentially therapeutic approach proposed by Brown-Séquard. After Murray's discovery, new investigative techniques were found to be both applicable and necessary. A new rigor was

³⁶¹ Charles-Éduard Brown-Séquard, "On a New Therapeutic Method Consisting in the Use of Organic Liquids Extracted from Glands and Other Organs," *British Medical Journal* 1 (1893): 1145–1147, 1212–1214.

³⁶² William Miller Ord, "On the French 'Method' of Organotherapy," *Transactions of the Clinical Society of London* 23 (1890): 214.

³⁶³ George Redmayne Murray, "Notes on the Treatment of Myxoedema," *British Medical Journal* (1891): 796–797.

achieved on at least one front: It was recognised that the problem of what constituted clinical proof of a cure of a disease had to be directly confronted. Awareness of this issue had then encouraged the re-examination of a second important problem: how best to measure the therapeutic effects of organ extracts. It became clear that the experimental system employed by investigators needed to use models that were simpler than the diseased human body, and the system needed to be quantifiable.

During the decade of the 1890s, investigations concerning internal secretions were gradually removed from the clinic to the laboratory. Specific questions were asked by investigators and standard physiological techniques were employed to answer them. Much of this methodological revaluation developed quite naturally out of the discoveries of Murray.³⁶⁴ It is for this reason that Murray's findings were generally perceived as landmarks, both in the cure for myxoedema as well as the acceptance of organotherapy, and ultimately the concept of organ replacement therapy.

The genealogical continuity of studies relating to internal secretions is far less obvious in the British than in the French medical literature. Even after reading the original research report of Murray, one is apt to view the discovery of therapeutically-active thyroid extracts as quite a distinct and unrelated event, unless one is aware of the therapeutic movement which was already underway when this discovery was made. Part of the apparent lack of continuity is due to the discontinuity introduced by the methodological considerations outlined above.

To understand the context of Murray's discovery, it is necessary to review briefly the reception in England of Brown-Séquard's ideas on internal secretion and to point out how the British medical profession maintained a sceptical attitude towards these ideas and the

³⁶⁴ Another important discovery during that time that aided research in the curative characteristics of animal extracts was the observation in 1894 of the vasopressor effects of adrenal extract by George Oliver (1841-1915) and Edward Sharpey-Schäfer (1850-1935).

evidence advanced to support them. In retrospect, it is clear that a new kind of evidence was required to generate any widespread interest in organotherapy in Britain.

4.3. BRITISH PHYSICIANS AND ‘INTERNAL SECRETION’

The precise impact in Britain of Brown-Séquard’s experiments with testicular extract is difficult to assess from the reports published in the leading British medical journals such as the *British Medical Journal* or the *Lancet*. Few relevant reports were published between 1889 and 1891, and they tell us little of the response of British physicians, except by implication. Nonetheless, it is evident from later communications that some British physicians were interested in the phenomena described by Brown-Séquard, and that some work on the therapeutic effects of testicular extract was subsequently undertaken.

On June 22, 1889, three weeks after Brown-Séquard’s first communication to the Society of Biology in Paris, the *British Medical Journal* published an account of the phenomenon of rejuvenation reported by the French physician. In an article entitled “The Pentacle of Rejuvenescence,” the journal described Brown-Séquard’s experiments with testicular extract.³⁶⁵ Although the discussion of the experiments was fairly straightforward, preliminary comments in the report suggest that the popular reaction to the public announcement of Brown-Séquard’s ‘discovery’ had been quite unsettling for the medical profession. The report lamented that the statements made by the French researchers would “recall the wild imaginings of medieval philosophers in search of an *elixir vitae*.”³⁶⁶ Here, the choice of title is in itself an indication of the disbelief with which Brown-Séquard’s results were received, with the term “pentacle” referring to a symbol in magic, the five-pointed star.

³⁶⁵ British Medical Journal, “The Pentacle of Rejuvenescence,” *British Medical Journal* no. 1 (1889): 1416.

³⁶⁶ Ibid.

In the twenty-three line report, there was no mention of the request Brown-Séquard had made, urging other experimenters to test the “spermatic fluid.” It contained only an inclusion of the summary of the opinions of the Parisian physicians Jacques Fere and Jean Dumontpallier that they required Brown-Séquard’s claims to be “rigidly tested and fully confirmed by other self-experimenters before they were likely to meet with general acceptance.”³⁶⁷ The editors of the *BMJ* merely commented that “in this opinion” they “fully” concurred.³⁶⁸

Thus, although enthusiasm for the testicular extract developed in other countries during the next few months, notably in France, Russia, and the United States, and Brown-Séquard reported on the therapeutic successes of the fluid to his colleagues in Paris, no comparable interest appears to have been generated in Britain. In fact, only two foreign reports of treatments with the testicular extract were cited by the *BMJ* in 1889. The first summarised the results of the physician Gaston Variot in Paris on the treatment of senile debility;³⁶⁹ the second relayed an unconfirmed report from Indianapolis.³⁷⁰

A thirteen-line report concerning Variot’s successful treatment of three debilitated men with testicular extract was published by the *BMJ* on July 6, 1889.³⁷¹ It stated that, based on these cases, Brown-Séquard had concluded that: “Variot’s observation disposed of the objection that the results he [Brown-Séquard] had observed in himself were due to ‘suggestion.’”³⁷² There was no indication that the editors of the *BMJ* shared this view. Six weeks later in an article of but eight lines, the same journal described a report from Indianapolis which claimed

³⁶⁷ Ibid.

³⁶⁸ Ibid.

³⁶⁹ G. Variot, “Trois experiences sur l’action physiologique du suc testiculaire injecté sous la peau, suivant la method de M. Brown-Séquard,” *Comptes rendus de Société de Biologie* 1 (1889): 451–454.

³⁷⁰ British Medical Journal, “The New Elixir of Youth,” *British Medical Journal* no. 2 (1889): 446.

³⁷¹ British Medical Journal, “Dr. Brown-Séquard’s Hypodermic Fluid,” *British Medical Journal* no. 2 (1889): 29.

³⁷² Ibid.

that “Dr. Brown-Séquard’s rejuvenating fluid” had invigorated a “decrepit old man.”³⁷³ The article indicated that no “medical authority” had been provided, implying that the observation had yet to be confirmed. It is apparent that the *BMJ* maintained a sceptical attitude towards such reports from abroad. The sensational nature of Brown-Séquard’s rejuvenating claims, the possibility that these results were the outcome of suggestion, and the lack of reliable confirming data seemed to make this stance appropriate in 1889.

However, two letters published in the *BMJ* during this period suggest that an insufficiency of data was not the only reason for the caution with which Brown-Séquard’s ideas were received in Britain. At least two other factors were also important: firstly, the outrage among antivivisectionists who objected to the use of extracts of animal organs;³⁷⁴ and, secondly, the outrage of some members of the medical profession who objected not only to the injection of seminal fluid of animals into human beings, but who also abhorred the possibility that the rejuvenating treatment of Brown-Séquard involved masturbation.³⁷⁵ One such member of the medical profession had by July 7, 1889, published 6000 copies of a circular which protested against the experiments of Brown-Séquard on both grounds. The *BMJ* had responded to the circular and criticised the naivety of the author regarding the general use of castrated animals in the meat industry.³⁷⁶ The journal did not comment, however, on the moral objections raised by the unnamed author, who repeated those objections in his letter to the editor six weeks later.³⁷⁷

³⁷³ British Medical Journal, “The New Elixir of Youth.”

³⁷⁴ The context for such attitudes is described in French, *Antivivisection and Medical Science in Victorian Society*.

³⁷⁵ This criticism probably refers to the fact that Brown-Séquard observed that if debility were due to seminal loss, increased vigour might result from seminal retention. He had advocated sexual excitement without ejaculation to some of his patients.

³⁷⁶ British Medical Journal, “The Recent Experiments of Dr. Brown-Séquard,” *British Medical Journal* 2 (1889): 229. The journal claimed that its objections were quoted out of context by the author of this tract and, further, that the charges of barbarity were not justified as it was common agricultural practice to castrate animals to improve the flavour of the meat.

³⁷⁷ British Medical Journal, “Dr. Brown-Séquard’s Experiments: A Member of the Medical Profession Writes,” *British Medical Journal* 2 (1889): 347.

The summary of the unconfirmed report from Indianapolis cited above was published two weeks after this letter appeared, but no additional articles on the subject of testicular fluids were published in the *BMJ* in either 1890 or 1891.

The response in the *Lancet* during those years appears equally subdued. In 1889, the journal published only one article, written by Brown-Séquard relating to experiments with the testicular extract.³⁷⁸ The editors of *The Lancet* responded to him on July 10, 1889. As their letter indicates, they too had become concerned by the sensational reports in the public press. They stated that they had not yet published an account of any kind regarding the therapeutic power of the testicular liquid precisely because of the sensationalist and “no doubt inaccurate” nature of the accounts provided by the daily press.³⁷⁹

The next year, Brown-Séquard sent a two-page article entitled “Note on the effects produced on man by subcutaneous injections of a liquid obtained from the testicles of animals,”³⁸⁰ from Brighton where he was visiting in the summer of 1889. It concluded with his familiar exhortation, that “[w]hatever may be thought of these speculations [regarding the aging process] the results I have obtained by experiments on myself ... show that this important subject should be further investigated experimentally.”³⁸¹

³⁷⁸ Charles-Éduard Brown-Séquard, “Note on the Effects Produced on Man by Subcutaneous Injections of a Liquid Obtained from the Testicles of Animals,” *The Lancet* 2 (1889): 105–107. This paper is essentially a review of Brown-Séquard’s three notes to the French Society of Biology; see: Brown-Séquard, “Des effets produits chez l’homme par des injections sous-cutanées d’un liquid retire des testicules de cobaye et de chien”; Charles-Éduard Brown-Séquard, “Seconde note sur les effets produits chez l’homme par des injections sous-cutanées d’un liquid retire des testicules frais de cobaye et de chien,” *Comptes rendus de Société de Biologie* 1 (1889): 420–422; Charles-Éduard Brown-Séquard, “Troisième note sur les effets des injections sous-cutanées de liquid testiculaire,” *Comptes rendus de Société de Biologie* 1 (1889): 430–431. Brown-Séquard reported the appearance of the *Lancet* article to his colleagues in the Society of Biology on October 5, 1889. The article provides an excellent summary of Brown-Séquard’s ideas concerning the testicular fluid.

³⁷⁹ The *Lancet*, “Before Our Time,” *The Lancet* 1 (1865): 315.

³⁸⁰ Brown-Séquard, “Note on the Effects Produced on Man by Subcutaneous Injections of a Liquid Obtained from the Testicles of Animals,” 106–107.

³⁸¹ *Ibid.*

On January 4, 1890, the *Lancet*'s New York correspondent described the controversy raging in the United States over the efficacy of the testicular extract in "renewing the vigour of youth in the aged."³⁸² The opening sentences of the article suggest the disbelief with which the correspondent witnessed the vigorous response in America.³⁸³ However, no British reports on the testing of the testicular extract were published in *The Lancet* in either 1890 or 1891.

Certainly, Brown-Séquard's scientific reputation in Britain cannot be judged solely from these few published responses to his studies on the physiological and therapeutic effects of testicular extract. Brown-Séquard had travelled extensively between 1852 and 1872. He had lectured and held positions in Britain and America as well as in Paris. His neurological and physiological work was well known to British physicians and physiologists. In fact, the eleventh edition of the *Encyclopaedia Britannica*, published in 1910, refers to him as the "British physiologist and neurologist."³⁸⁴ Brown-Séquard was, therefore, not without colleagues and friends in Britain. Moreover, it is evident from his correspondence with d'Arsonval that the testicular extract was being sent to and tested by several Englishmen.³⁸⁵

Although there is no mention of such shipments to Britain prior to 1891, there are several references to the correspondence between Brown-Séquard and d'Arsonval beginning in February 1891 which indicate that testicular extract was being shipped to London by parcel post. In a letter of February 13, 1891, d'Arsonval commented on the receipt of a letter from Dr. Fanton-Cameron of London, presumably a request for the testicular extract.³⁸⁶ Six days later he wrote to Brown-Séquard that the most rapid and inexpensive way to send material to

³⁸² The *Lancet*, "Brown-Séquard's 'Elixir of Life' (New York, from Our Correspondent)," *The Lancet* 1 (1890): 57–58.

³⁸³ Ibid.

³⁸⁴ *Encyclopaedia Britannica*, "Charles Edward Brown-Séquard," in *Encyclopaedia Britannica*, vol. IV, 11th ed., 1910, 674.

³⁸⁵ See the correspondence between February 3 and May 4, 1891, cited below. Léon Delhoume, *De Claude Bernard a d'Arsonval* (Paris: J.-B. Baillière, 1939), 402.

³⁸⁶ Letter of February 13, 1891, *Ibid.*, 360.. D'Arsonval wrote, "I have sent some liquid to Dr. Jacquard, I have likewise received a letter from London from Dr. Fanton-Cameron; I await your orders to dispatch [it]."

London was by parcel post.³⁸⁷ Then, in four consecutive letters written between February 17 and 22,³⁸⁸ Brown-Séquard gave d'Arsonval instructions for sending the testicular liquid to London, asking him to send some to Drs. Fanton-Cameron, Brudenell Carter,³⁸⁹ and also to Victor Horsley, then Assistant Professor of Pathology at University College, London. In the letter of February 25, d'Arsonval reported that he had sent two bottles to each of them.³⁹⁰

Curiously, on February 26th, Brown-Séquard wrote to d'Arsonval, "I regret that you have sent some 'liquid' to Horsley; he will not know what to do with it and will be very surprised. That which I have asked you (and I did it in two letters) was to forward him a sample of the no. of comptes rendus containing your work on filtration by the aid of carbon dioxide."³⁹¹ There is no further record of these exchanges with Fanton-Cameron, Carter, or Horsley; only the suggestion by Brown-Séquard on March 29 that it would be good if d'Arsonval were to show the laboratory to Horsley, who was at Paris for the Congress of Surgery. Horsley's response to this invitation or to the receipt of the extract has not been recorded.³⁹²

On April 10 and 14 and May 3, Brown-Séquard asked d'Arsonval to send bottles of the testicular liquid to his old friend and wife's cousin, Dr. W. D. Waterhouse of London.³⁹³ Waterhouse wished to procure all the equipment necessary to make the liquid, and thus Brown-Séquard directed d'Arsonval to ship the equipment to him. Waterhouse's report on

³⁸⁷ Letter of February 19, 1891. Ibid., 364.

³⁸⁸ Ibid., 365. Unfortunately, these letters were not published. Delhoume, editor of the correspondence, noted in a footnote: "Brown-Séquard, in four consecutive letters from the 17 to 22 of February, gives some directions to d'Arsonval for the shipments of testicular fluid to England and requests him notably to address some Doctors Fanton-Cameron, Brudenell Carter and Professor Horsley, of London."

³⁸⁹ Robert Brudenell Carter (1828-1918) was an ophthalmic surgeon. He served on the staff of both *The Lancet* and *The Times*. See: d'Arcy Power, "Robert Brudenell Carter," in *Plarr's Lives of the Fellows of the Royal College of Surgeons of England*, vol. 1 (London: Royal College of Surgeons, 1930), 201-203., and *British Medical Journal*, "R. Brudenell Carter, R.R.C.S.," *British Medical Journal* 2 (1918): 502-503.. I have been unable to locate any biographical material on Fanton-Cameron.

³⁹⁰ Delhoume, *De Claude Bernard a d'Arsonval*, 366.

³⁹¹ Letter of February 26, 1891, Ibid., 368-369.

³⁹² Letter of March 29, 1891, Ibid., 385.

³⁹³ Ibid., 394, 396-397, 402. Apart from this mentioning of Waterhouse's name, I have been unable to procure any information about him.

the use of the extract did not appear in the *BMJ* until January 30, 1892,³⁹⁴ at which time organotherapy was becoming an acceptable mode of therapeutics in Britain. To understand this growing respectability of organotherapy in 1892, one must turn to the progress of work on the thyroid gland, work in which the surgeon Victor Horsley played a prominent role once again.

4.4. THE THERAPEUTIC TURNING POINT

The therapeutic turning point in the way myxoedema was understood came in 1891, when George Redmayne Murray announced that he had “treated myxoedema successfully, resulting in the disease’s striking symptoms to almost completely subside.”³⁹⁵ In a letter dated October 1890, Victor Horsley reported to Murray a novel theory proposed in France by Brown-Séquard and d’Arsonval regarding the therapeutic use of liquid extracts gained from animal organs in the treatment of disease, which the French duo had labelled organotherapy.³⁹⁶ Horsley proposed that it might be worthwhile to investigate the action of these substances by using extracts of specific tissues to treat a certain disease. He argued that should a given condition be successfully treated by the use of such a tissue extract, it was likely that the condition itself was caused by inadequate production of an internal secretion from the corresponding organ.³⁹⁷ Motivated by this argument, Murray used the liquefied thyroid gland of sheep to treat a female patient with severe myxoedema by means of subcutaneous injections. He based his work on the hypothesis of Horsley that the lack of thyroid function brought the disease about, as discussed in the preceding chapter. The

³⁹⁴ British Medical Journal, “Report of the Clinical Evening of the Harveian Society,” *British Medical Journal* 1 (1892): 22. Waterhouse was the cousin of Brown-Séquard’s third wife; see: J.M.D. Olmsted, *Charles-Édward Brown-Séquard: A Nineteenth Century Neurologist and Endocrinologist* (Baltimore: Johns Hopkins Press, 1946), 229.

³⁹⁵ The results were first presented at the Durham-Newcastle Medical Society in 1891 and published in the *British Medical Journal* the same year; Murray, “Notes on the Treatment of Myxoedema,” 797.

³⁹⁶ Victor Alexander Hayden Horsley, “MS Copies of Letters Sent from Victor Horsley to George Murray,” MMC/2/MurrayG/1/4, 1890, John Rylands University Library of Manchester.

³⁹⁷ The events that led up to this proposal have been discussed in Borell, “Organotherapy, British Physiology, and Discovery of the Internal Secretions.”

ultimate improvement of the patient's condition led Murray to confirm Horsley's theory that a deficiency of this organ was the cause of myxoedema.³⁹⁸

Murray was a physician, not a physiologist, but as an academic doctor in a university setting, he was used to applying the methods of experimental physiology to his work.³⁹⁹ Other researchers, like Horsley, had been trying to link the thyroid to myxoedema using animal experiments by complete surgical removal of the organ. However, earlier thyroidectomies in animals had been either incomplete or brought on a quick death for the test subject. Horsley's problem, as discussed in Chapter 3, was his inability to demarcate effectively between myxoedema and Theodor Kocher's *cachexia strumipriva*, thus being unable to show the causal link between the ceasing of a presumed thyroid function and the onset of myxoedematous symptoms. Therefore, strictly speaking, no one prior to Murray had ever observed what would happen if, after complete thyroid failure—either naturally, through disease, or artificially through surgical thyroidectomy—the function of the organ was restored, and no one had seriously considered that the organ could have another physiological function other than hypothetical haematopoiesis, i.e. the formation of blood.⁴⁰⁰

Prior to his 1891 therapeutic procedure, this possibility had not entered the mind of Murray either. He had worked meticulously to apply the latest experimental standards. He carefully removed the thyroid from the donor sheep, put it to rest on ice and examined it meticulously for any redundant tissue. His aim was to examine the effect of a pure liquefied thyroid gland, as free from any potential influences from foreign tissue as possible.⁴⁰¹ After preparing the

³⁹⁸ George Redmayne Murray, "The Clinical History and Symptoms of 120 Cases of Exophthalmic Goitre," *The Lancet* no. 1 (1902): 615; Horsley, "Remarks on the Function of the Thyroid Gland: a Critical and Historical Review," 217.

³⁹⁹ Murray read for his medical degree at University College London and during his final year worked closely with Victor Horsley, who introduced him to experimental physiology.

⁴⁰⁰ One has to be careful here with the term 'function,' as Murray's clinical experiment, though relying on a function of the thyroid, cannot determine the *sine qua non* function of the organ.

⁴⁰¹ George Redmayne Murray, "The Treatment of Exophthalmic Goitre and Other Forms of Hyperthyroidism," *The Lancet* no. 1 (1923): 112.

thyroid juice, Murray took care to immediately cease any other medication his patient took for her myxoedematous or other symptoms in order to rule out reciprocation of pharmaceutical substances, even allowing for a period of seven days to purge her body of any residual quantities of her previous medicines.⁴⁰² He later concluded that it was above all his adherence to this strict procedure that had made his feat not just possible, but above all persuasive. After all, the patient who underwent this procedure was not susceptible to the interaction of medicines, taking only pure thyroid juice, thus ruling out any possible foreign or unintended pharmaceutical agent as the cause for the beneficial therapeutic changes in her condition.

At the beginning of spring 1892, Murray performed the same procedure on five more female patients. Shortly after commencing the therapy, the patients not only improved in their overall clinical picture but also started menstruating again.⁴⁰³ Horsley, Murray's former teacher at UCL planned further trials in experimental physiology in order to clarify whether his student had really discovered the cause of myxoedema.⁴⁰⁴ If so, then the absence of the thyroid—or, by extension, the thyroid's lack of function—was the necessary cause of myxoedema. Controlling this cause would henceforth mean controlling the disease.

As was the case with the preliminary results gathered by the Clinical Society's myxoedema committee, criticism was to be expected mainly from those medical scientists who believed that myxoedema was caused by some disturbance of the nervous system.⁴⁰⁵ In order to invalidate such criticism tighter control over the phenomena observed needed to be achieved. To begin with, medical scientists had to isolate the presumed organ function more precisely to prove that any phenomena observed could, by extension, be attributed to the

⁴⁰² Ibid.

⁴⁰³ Murray, "The Clinical History and Symptoms of 120 Cases of Exophthalmic Goitre."

⁴⁰⁴ Horsley, "Thyroid"; Horsley, "Experimental and Clinical Contributions of Thyroid Tissue Replacement."

⁴⁰⁵ I will review such a dispute in section 8 of this chapter.

absence of the organ itself. In order to show that other lesions in the body did not play a particularly important part, Horsley separated the thyroid from its original site, leaving intact only one artery to guarantee its blood supply. In contrast to the laboratory animals he had used for his committee research, the new test subjects did not develop myxoedematous symptoms, despite extensive damage to possible neural connections.⁴⁰⁶

Nevertheless, there was yet another objection to refute. After Horsley's experimental results, which were in turn based on Murray's assumptions, became disseminated, other researchers became involved and, based on similar experiments of their own, proposed the thesis that the observed myxoedematous symptoms after complete thyroid removal had little to do with the absence of the gland itself, but rather with the relative loss of fresh, new blood being delivered to the body.⁴⁰⁷ This objection is of course based on the assumption that the thyroid gland acts as a haemopoietic organ. The obvious counterargument here, i.e. that haemopoiesis could itself be interpreted as a true function of the thyroid, was not contended by this group. The issue rather seems to have been Murray's, and by extension Horsley's, claim that the thyroid gland might have a function relating to the concept of 'internal secretions,' which I will discuss later in this chapter. The only way to counter this supposition was to isolate the organ further: namely by separating the thyroid gland from its original site, thus attempting to disprove the objection based on nerve damage, as well as on haemopoeisis. Horsley, therefore, removed a piece of the organ, this time together with the vessels that provided its blood supply, from the neck to a location under the skin of the

⁴⁰⁶ Horsley, "Some Researches Carried Out During the Last Ten Years into the Functions of the Brain and the Thyroid Gland"; Sheryl R. Ginn and Joel A. Vilensky, "Experimental Confirmation by Sir Victor Horsley of the Relationship Between Thyroid Gland Dysfunction and Myxedema," *Thyroid* 16 (2006): 743–747.

⁴⁰⁷ This group largely recruited itself from Manchester and Oxford based clinicians and scientists. An overview of their arguments and conclusions can be gathered from: Lancaster, "Notes and Reflections on the Thyroid and Its Relation to Disease"; William S. Halsted, *An Experimental Study of the Thyroid Gland of Dogs, with Especial Consideration of Hypertrophy of This Gland* (Baltimore: Johns Hopkins Press, 1896); British Medical Journal, "Thyroid Extract in Myxoedema," *British Medical Journal* 1 (1893): 252.

abdomen of a monkey. After this partial graft had taken, he removed the rest of the remaining thyroid tissue from the neck, so that any of its supposed haemopoietic function at that site could no longer take place. The results showed that the absence of the alleged haemopoietic function of the thyroid, in connection with possibly severe nerve damage to the surrounding tissues at the original site, did not produce myxoedema in his test subjects, as long as the abdominal transplant was not removed.⁴⁰⁸ Thus, this method of experimentation also allowed for studying the effects of the operation on the nervous system in complete isolation from the effects of radical thyroidectomy. After transplanting the thyroid of a laboratory animal to another suitable site inside its body, the same lesions were present around the natural site as after straightforward surgical thyroidectomy, as for example practiced in Switzerland by Kocher. However, neither myxoedematous symptoms nor *cachexia strumipriva* occurred as long as there was still thyroidal tissue present elsewhere in the body. Horsley expressly pointed out the analogy between his procedure and the similarities to the corresponding experiments by Moritz Schiff and von Eiselsberg.⁴⁰⁹

In the years to follow, the role of the function of the thyroid gland was questioned repeatedly; experimental—and by extension clinical—findings were either doubted or, as happened more commonly, variously interpreted. Despite Murray's successes and Horsley's experimental transplantations, the idea of a neurogenic origin of myxoedema persisted, as did the explanation that the disease's striking symptoms resulted from the fact that the haemopoietic function of the thyroid could no longer take place.⁴¹⁰ Part of the reason for the apparent reluctance to be persuaded by these results was their experimental confirmation.

⁴⁰⁸ Horsley, "Some Researches Carried Out During the Last Ten Years into the Functions of the Brain and the Thyroid Gland"; Ginn and Vilensky, "Experimental Confirmation by Sir Victor Horsley of the Relationship Between Thyroid Gland Dysfunction and Myxedema," 746.

⁴⁰⁹ Kocher's thyroidectomies as well as Schiff's and von Eiselsberg experimental work have been discussed in Chapter 1.

⁴¹⁰ See for example, Otto Lubarsch, "Über Gewebsembolien und Gewebsverlagerungen," in *Verhandlungen der Deutschen Pathologischen Gesellschaft* (Berlin: Fischer, 1899), 97–103.

Experiments of this kind were technically difficult. A radical thyroidectomy without causing the death of the laboratory animal demanded not only the right specimen, but also great technical skill and experience; and even then, given all those components came together, it did not always work. The pathologist Joseph Ransohoff (1853–1912) at Guy's Hospital, London, for example, attempted to replicate Horsley's procedure and moved parts of the thyroid to a location in the abdominal wall. However, he was unable to keep his experimental animals alive after removing all of the remaining thyroid tissue in the neck after the graft had taken.⁴¹¹

Thus, experimental or clinical confirmation of Horsley's experiments could not be obtained; accordingly, Murray's findings on the viability of the thyroid as the causal agent in the pathogenesis of myxoedema, as opposed to a neurogenic cause, did not convince the majority of his peers. To understand some of these objections, it is worth taking a brief look at the development of the concept of organotherapy, which directly led up to Murray's clinical experiment of 1891. The nature of which, although highly contested at the time, was certainly necessary for the conception not only of Murray's treatment for myxoedema, but also for thyroid replacement therapy in general.

4.5. THYROID EXTRACT AND THE TREATMENT OF MYXOEDEMA

Horsley had been a member of the committee appointed by the London Clinical Society in 1883 to investigate experimentally the relationship between the conditions of Myxoedema, cretinism, and *cachexia strumipriva*.⁴¹² In that year, as we have seen in Chapter 1, Reverdin and Kocher extirpated the thyroid for the treatment of goiter and reported that the condition (later to be called *cachexia strumipriva*) supervened after total thyroidectomy. The same year,

⁴¹¹ Joseph Ransohoff, "On the Normal and Pathological Morphology of the Thyroid," *Annals of Surgery* 19, no. 1 (1894): 78–84.

⁴¹² We have discussed this in Chapter 3.

Felix Semon stated that this condition was similar to the myxoedematous state first indicated by William Gull in 1873 and later by William Ord in 1878. He also asserted that it appeared highly probable that the three conditions were related to disturbed thyroid function, and the London Clinical Society undertook a study of this question.⁴¹³

Horsley was on the surgical staff of both University College Hospital and the National Hospital for the Paralyzed and Epileptic when d'Arsonval shipped the vials of testicular extract to him. He was no longer directly engaged in experimental work on the thyroid gland; that had occupied him principally during the years 1884-88. He had since turned his attention to the prevention of rabies in England and had begun studies on the localisation of brain functions.⁴¹⁴

Nonetheless, in February of 1890, following the report of successful grafting of thyroid glands into thyroidectomised animals, Horsley advocated the grafting of thyroid tissue into myxoedematous patients as a treatment for the disease.⁴¹⁵ This was an idea which his former student Murray implemented by successfully treating a myxoedematous patient with subcutaneous injections of thyroid juice.

Murray had been a student and house physician at University College Hospital from 1886 until 1889. He had attended Horsley's course of practical pathology, as well as Horsley's outpatient practice. The young student had set his mind "upon a career in experimental medicine" and "for this purpose he visited the most famous of the medical clinics in Berlin and Paris."⁴¹⁶ Horsley provided him with letters of introduction, and Murray toured clinics on the Continent

⁴¹³ This has been dealt with at length in Chapters 2 and 3.

⁴¹⁴ Edwin Clarke, "Victor Alexander Haden Hayden Horsley," in *Dictionary of Scientific Biography*, ed. C. C. Gillispie, vol. VI (New York: Charles Scribner's Sons, 1972), 518–519. See also Paget (1920). Horsley was also Assistant Professor of Pathology at University College, London.

⁴¹⁵ Horsley (1890).

⁴¹⁶ Spence (1949) and Paget, *Sir Victor Horsley*, 65–66.

between 1889 and 1890. It is possible that while in Paris he became acquainted with the therapeutic trials being made with testicular extract.

After Murray settled in Newcastle-Upon-Tyne as pathologist to the Hospital for Sick Children, he began to correspond with Horsley.⁴¹⁷ They corresponded regarding the feasibility of injection experiments with thyroid juice. In a letter from December 3, 1890, Horsley advised his protégée that up until this point experiments involving liquefied glands “have only produced slight results ... However, it cannot do any harm, and I think it would be worth trying, as it is possible from Schiff’s results of imperfect transplantation that an emulsion of the gland might possess some of its active properties.”⁴¹⁸

On June 22, 1891, Horsley brought Murray up to date on the current literature regarding thyroid disorders, citing the work of Vassale and of the Spanish investigators Bettencourt and Serrano. Upon enquiry, Serrano assured Murray that the article contained “only a suggestion, not the actual practice [of treating myxoedema]. In that, you have only been forestalled experimentally.”⁴¹⁹ However, he mentioned neither Eugene Gley’s work, nor that of Brown-Séquard and d’Arsonval, which had been published the previous April.

Murray reported his observations on the treatment of Myxoedema with thyroid juice within the month. His “Note on the treatment of Myxoedema by hypodermic injections of an extract of the thyroid gland of a sheep” was read in the Section of Therapeutics at the Annual Meeting of the British Medical Association held in Bournemouth in July 1891. The paper was published in the *BMJ* on October 10, 1891.⁴²⁰ There was no reference in this paper to the generalised notion of internal secretions advanced in the previous April by Brown-Séquard

⁴¹⁷ Murray also held the post of lecturer in bacteriology at the Durham University College of Medicine.

⁴¹⁸ Cited in Paget, *Sir Victor Horsley*, 65–66. It is interesting to note that Horsley abstained from mentioning his own research, which would have been well known to Murray anyhow.

⁴¹⁹ *Ibid.*, 66.

⁴²⁰ Murray, “Notes on the Treatment of Myxoedema.”

and d'Arsonval, but it contained Murray's account of the historical route by which the idea had occurred to investigators that the loss of thyroid function could be remedied by injections of juice of the thyroid.⁴²¹

Murray stated: "The observations of the symptoms which followed the removal of the thyroid gland in man made by Professor Kocher, of Berne, and the results of the experimental removal of the gland in monkeys obtained by Mr Victor Horsley have firmly established the view that this disease Myxoedema is due to the loss of function of the thyroid gland."⁴²² He also mentioned the experiments of von Eiselsberg showing that transplantations of the thyroid to another part of the body prevented the onset of many of the usual symptoms which followed total thyroidectomy. He also cited the article in the *BMJ* of February 8, 1890, in which Horsley had suggested the grafting of a sheep's thyroid into a myxoedematous patient.

Such a graft had been successfully carried out by Bettencourt and Serrano of Lisbon, as reported by them in *La semaine médicale* on August 13, 1890. According to Murray, "these authors considered that as the improvement commenced the day after the operation, it could not be due to the gland becoming vascularised and so functional, but suggested that it was due to the absorption of the juice of the healthy thyroid gland by the tissues of the patient."⁴²³ Murray concluded that it would seem "reasonable to suppose that the same amount of improvement might be obtained by simply injecting the juice or an extract of the thyroid gland beneath the skin of the patient."⁴²⁴ Furthermore, he observed, "if we consider that Myxoedema and cachexia strumipriva are due to the absence from the body of some

⁴²¹ Note that Murray credited Horsley while Abelous said that Bouchard recommended this treatment as early as 1887; see J. E. Abelous, "La physiologie des glandules à sécrétion interne: Corps thyroïde et capsules surrénales," *Revue Générale des Sciences Pures et Appliquées* 4 (1893): 275.

⁴²² Murray, "Notes on the Treatment of Myxoedema," 796. Murray was referring to Horsley's conclusions in the Brown Lectures of 1885.

⁴²³ *Ibid.*, 797.

⁴²⁴ *Ibid.*, 796.

substance which is present in the normal thyroid gland, and which is necessary to maintain the body in health, it is at least a rational treatment to supply that deficiency as far as possible by injecting the extract of a healthy gland.”⁴²⁵ Murray gave no clear indication as to how such a substance might “maintain the body in health.” He only proposed a “rational treatment” which should be tried to treat such a deficiency.

Murray cited Vassale’s work on the intravenous injection of thyroid extract into thyroidectomised dogs but did not indicate any knowledge of Eugene Gleys’ corresponding study, published in the *Comptes rendus* of the Society of Biology for April 18, 1891.⁴²⁶ He believed his own work to be the first attempt to use this treatment on a human subject and remarked that he had already suggested this treatment at a meeting of the Northumberland and Durham Medical Society. Apparently, the use of thyroid extract as a medicament was “in the air” in the winter of 1890-1891.⁴²⁷

Murray’s treatment of a myxoedematous patient by the subcutaneous injection of thyroid juice in 1891 was the first generally acknowledged clinical success of organotherapy. Moreover, thyroid pathology was one of the first on-going research problems to which the notion of internal secretion was directly applicable. Acknowledging analogies already pointed out by Brown-Séquard and d’Arsonval, British physicians soon began to test other organ extracts.

⁴²⁵ Ibid.

⁴²⁶ Eugène Gley, “Note préliminaire sur les effets physiologiques du suc de diverses glandes et en particulier du suc extrait de la glande thyroïde,” *Comptes rendus de Société de Biologie* 3 (1891): 250–251.

⁴²⁷ Letter of April 16, 1891, Brown-Séquard to d’Arsonval, Delhoume, *De Claude Bernard a d’Arsonval*, 400. Brown-Séquard urged d’Arsonval to present a communication to the Society of Biology on the following Saturday because “the thing is in the air—especially in Italy.”

4.6. A “RATIONAL” THERAPY

Murray’s note to the British Medical Association on the use of thyroid extract in the treatment of myxoedema was followed by a paper on “The diurectic action of fresh thyroid juice,” by E. Harry Fenwick, Surgeon to the London Hospital and St. Peter’s Hospital.⁴²⁸ During the previous year (1890), Fenwick had grafted a sheep’s thyroid into a myxoedematous patient. He had split the gland prior to grafting and rubbed the secretion into the subcutaneous tissue. The next day the patient’s temperature rose, and urine output increased one hundred and fifty per cent. Fenwick, not being certain that these effects were due to “the absorption of the free secretion of the thyroid,” attempted hypodermic injection of the juice in his next patient. The diurectic effects following the injections were so striking that he suggested that “the state known as Myxoedema depends upon a perverted renal function.” He argued, “[b]efore submitting our patient and results to the Clinical Society we would wish that so simple an injection is tried in order that rebutting or confirming evidence might be brought forward at the same time.”⁴²⁹ Additional data on the effects of thyroid injections were soon forthcoming.

British physicians published numerous reports on the administration of thyroid juice in the treatment of myxoedema during 1892. In the midst of these publications, Victor Horsley’s two-part article, “Remarks on the function of the thyroid gland: an historical review,” appeared on January 30 and February 6 of 1891.⁴³⁰ Clinical reports on the use of hypodermic injections in the treatment of myxoedema were published first by Beatty and Carter and later

⁴²⁸ E. Harry Fenwick, “The Diuretic Action of Fresh Thyroid Juice,” *British Medical Journal* 2 (1891): 798.

⁴²⁹ Ibid. Fenwick does not explain his interpretation. Presumably, he thought the accumulation of fluid to be due to a malfunctioning of the kidneys.

⁴³⁰ Horsley, “Remarks on the Function of the Thyroid Gland: a Critical and Historical Review.” This paper had appeared in German in 1891 in *Virchow’s Festschrift*.

by Murray, Fenwick, and Barron. Among these papers appeared reports by Mackenzie and Fox which showed that thyroid could be given effectively by mouth, as well as by injection.⁴³¹

These successes with the use of thyroid extract as a therapeutic agent led to the appearance of an editorial in the *BMJ* on October 29, 1892. A rational therapy for myxoedema had been discovered. The article proclaimed its surprise that “the recent experimental investigation of the functions of the thyroid gland, and especially that of the effects of its removal, would so soon have been applied with the most striking success in the treatment of a disease than which none had shown itself more absolutely intractable to all previous forms of treatment.”⁴³² Not only had there been several reports of success by subcutaneous injections of the extract, but now the gland itself could be orally administered to myxoedematous patients.

The success of thyroid therapy in the treatment of myxoedema soon led to the application of analogous reasoning to a similarly intractable disease, diabetes.⁴³³ Such sentiment appeared in a discussion following a paper on the pathology of the pancreas, written by Vaughn Harley (1863-1923), later Assistant Professor of Pathology at University College.⁴³⁴ This paper was presented at the 1892 meeting of the British Medical Association at which Murray presented an enlarged version of his report on the treatment of myxoedema by hypodermic injection of

⁴³¹ See the *BMJ* for the year 1892. The successful treatment of Myxoedema by feeding of fresh thyroid was reported in October.

⁴³² British Medical Journal, “The Treatment of Myxoedema,” *British Medical Journal* 2 (1892): 965.

⁴³³ For a more in-depth discussion of organotherapeutic treatment efforts in relation to diabetes, see: Michael Bliss, *The Discovery of Insulin* (Toronto: University of Toronto Press, 2007), 20–44.

⁴³⁴ Vaughan Harley, “The Pathogenesis of Pancreatic Diabetes Mellitus,” *British Medical Journal* 2 (1892): 452–454. Harley was the son of George Harley (1829-1896) who, under William Sharpey at University College, London, began the first class of Practical Physiology in England. The elder Harley was also the first to repeat Brown-Séquard’s experiments on adrenal extirpation; see: Sharpey-Schäfer, *History of the Physiological Society During Its First Fifty Years, 1876-1926*, 2.. According to papers published in the *Journal of Physiology*, Vaughan Harley was Assistant Professor of Pathology in 1895. He later became Professor of Chemical Pathology; see: *Ibid.*, 108..

thyroid juice.⁴³⁵ In the discussion after Harley's paper, the use of pancreatic juice was advocated for cases of diabetes. Harley remarked that extracts of the pancreas had been used in the treatment of diabetes, both in England and abroad, over the previous two years, but without success. His discussant, a physician by the name of Ransom, had tried similar experiments, also unsuccessfully.⁴³⁶ Such an analogy between the thyroid and the pancreas was drawn repeatedly over the next few months.

In December 1892, in a brief note entitled "Physiology in 1892," the *BMJ* called attention to the formerly unrecognised role of the two glands in the general metabolism. The possible parallel between the thyroid and the pancreas presented new and intriguing problems to physiology, because "investigators have confirmed that the glycosuria which follows extirpation of the pancreas can be stopped by transplantation of a portion of a living pancreas into the abdominal wall. This, taken in conjunction with the beneficial result that follows injection of the thyroid juice in myxoedema shows us that glands have actions in general metabolic processes which were before unknown but the modus operandi has yet to be discovered."⁴³⁷

Although such a parallel between thyroid and pancreatic physiology had already been pointed out by Brown-Séquard and d'Arsonval a year and a half earlier, the "hard" data supporting such a view of glandular function were only now beginning to emerge. Accordingly, organotherapy began to have a noticeable appeal in Britain.

⁴³⁵ George Redmayne Murray, "Remarks on the Treatment of Myxoedema with Thyroid Juice, with Notes of Four Cases," *British Medical Journal* 2 (1892): 449–450.

⁴³⁶ Harley, "The Pathogenesis of Pancreatic Diabetes Mellitus."

⁴³⁷ *British Medical Journal*, "Physiology in 1892," *British Medical Journal* 2 (1892): 1442.

Two brief reports of Brown-Séquard's testicular fluid appeared in the *BMJ* for 1892.⁴³⁸ In January, the above mentioned physician Waterhouse presented three cases of paralysis treated with testicular extract to the Harveian Society. In July, a brief letter, written by a Dr Ambrose, on the mode of preparations of Brown-Séquard's fluid also appeared. Ambrose's note did not directly advocate the use of testicular fluid, but its appearance in the *BMJ* highlights the new receptivity to the testing of the extract in the treatment of debilitating and nervous diseases.

Hector W. Mackenzie, one of the first to note the successful feeding of the thyroid gland in myxoedema, wrote that Mansell-Jones's experiments had already been preceded by Vaughan Harley in the previous year.⁴³⁹ And, in further response to Mansell-Jones' suggestion, Neville Wood of the Victoria Hospital for Children⁴⁴⁰ and W. Hale White of Guy's Hospital⁴⁴¹ each reported their separate experiences with the feeding of either raw pancreas or pancreatic juice in the treatment of diabetes. No one had yet cured diabetes with this mode of treatment—thus contrasting the organotherapeutic treatment of diabetes with the success in the treatment of Myxoedema; yet, the expectation of success caused this experiment to be repeated again and again.

4.7. ORGAN REPLACEMENT THERAPY AS A METHOD IN BRITAIN

In June of 1893, the *BMJ* published a two-part article by Brown-Séquard entitled "On a new therapeutic method consisting in the use of organic liquids extracted from glands and other

⁴³⁸ British Medical Journal, "Report of the Clinical Evening of the Harveian Society"; A. Ambrose, "Letter to the Editor in 'Letters, Notes, and Answers to Correspondents'," *British Medical Journal* 2 (1892): 163.

⁴³⁹ Hector W. G. Mackenzie, "The Treatment of Diabetes Mellitus by Means of Pancreatic Juice," *British Medical Journal* 1 (1893): 63–34. Mackenzie has already been mentioned in Chapter 2, in his capacity as one of the clinical physicians on the Myxoedema committee of the Clinical Society of London.

⁴⁴⁰ Neville Wood, "The Treatment of Diabetes by Pancreatic Extracts," *British Medical Journal* 1 (1893): 64.

⁴⁴¹ W. Hale White, "On the Treatment of Diabetes Mellitus by Feeding on Raw Pancreas and the Subcutaneous Injection of Liquor Pancreaticus," *British Medical Journal* 1 (1893): 452–453.

organs.”⁴⁴² In this paper, Brown-Séguard presented his data on the innocuity of these injections, and outlined his procedure for preparing the liquid organic extracts. He then proceeded to systematically review the data of the effects of kidney extract, liquid extract of the pancreas, hepatic extract, sex gland extracts, extracts of vascular glands, and the serum of dog’s blood. In his section on the “Mode of action of the various organic liquids,” he summarized that “it is very easy to understand how the cure is obtained when glandular liquid extracts are used; we simply give to the blood the principle or principles missing in it.”⁴⁴³

One week after the concluding half of Brown-Séguard’s paper appeared in press, the *BMJ* published a leading editorial, “Animal Extracts as Therapeutic Agents.”⁴⁴⁴ The editors noted that “these experiments [of Brown-Séguard] have been published before in various Continental journals, and readers of our EPITOME will have noticed week by week abstracts of these, as well as those by other workers on the same lines.” This comment confirms the novelty of such publications in Britain. The *BMJ* continued by referencing Brown-Séguard’s self-experiments with testicular fluid and the ridicule with which his ideas had initially been met. However, judging by “the success that has followed the injection of thyroid extract in Myxoedema, we can hardly wonder that this belief [in the viability of Organotherapy] has increased.”⁴⁴⁵

Not only had a belief in the efficacy of animal extracts as therapeutic agents increased, but the views of physiologists had been altered, too: “The experiments [...] have led to the introduction of the expression ‘internal secretion.’ We think that this term is a rather unfortunately chosen one; but it, nonetheless, expresses that the organs in question have

⁴⁴² Brown-Séguard, “On a New Therapeutic Method Consisting in the Use of Organic Liquids Extracted from Glands and Other Organs.”

⁴⁴³ *Ibid.*, 1213.

⁴⁴⁴ British Medical Journal, “Animal Extracts as Therapeutic Agents,” *British Medical Journal* 1 (1893): 1279.

⁴⁴⁵ *Ibid.*

some action on the blood, and through it on the tissues generally, which influences their metabolic changes.”⁴⁴⁶

Yet, the editorial became increasingly sceptical as, one by one, concerns about the current fascination with organ extracts were raised. The *modus operandi*, as well as the chemical composition of internal secretions, were yet undetermined. It was claimed that a temporary stimulating effect might well be expected from these extracts as they contained substances manufactured by the organism itself. In myxoedema, the curative result certainly justified the method used. However, fully granting this, the editors still felt “compelled to doubt many of the other so-called cures [as] we find medical men writing of these ideas and of the cures achieved in the most sanguine strain, and often upon no better evidence than quacks produce for their ‘cures’.”⁴⁴⁷

This editorial of the *BMJ* is thus indicative of the challenges that Brown-Séquard’s notions of both internal secretions and the resulting therapeutic approach of organotherapy faced; likewise, Murray’s more tangible results from his myxoedema trials. The whole notion of myxoedema being the result of a lack of internal thyroid secretion was questioned well into the first decade of the twentieth century, i.e. until after the development of the hormone concept in 1903. In the following section I will look at a telling example of this controversy, which essentially replayed the old debate between myxoedema being caused by a lack of thyroid function or by a nervous imbalance.

4.8. ORGAN REPLACEMENT THERAPY AND THYROID JUICE

During the 1890s, the promising treatment possibilities opened up by Murray’s discovery still rested on an unsatisfactory set of experimental data and the desperate situation of patients

⁴⁴⁶ Ibid.

⁴⁴⁷ Ibid.

with severe myxoedematous symptoms caused some doctors to resort to surgery to deal with the problem. In 1894, the London based surgeon Watson Williams published his attempt to treat a near hopeless case of myxoedema with thyroid transplants, expressly based on Horsley's experiments and Murray's idea. The operation was a xenotransplantation, i.e. a transplantation involving the thyroid from a non-human animal, in this case a sheep, and a human recipient. While the patient was anaesthetised with chloroform, Williams hurried to a neighbouring butcher and, under strictly aseptic conditions, removed the thyroid from a freshly slaughtered sheep. He cut the organ into three pieces and transplanted those into the subcutaneous tissue of the patient's chest and abdomen. The whole operation was over within twenty minutes of the sheep's death, but still proved to be unsuccessful. The patient died three days later in a coma whilst the transplants failed to take in the surrounding tissues, as the autopsy revealed. Williams attributed the patient's death and the failure of the transplants to the fact that the donor animal had been killed, according to customary slaughter proceedings, by bleeding to death. Should he carry out another such operation, he planned to use a donor sheep that was still alive.⁴⁴⁸ In a later comment, his explanation for the transplantation's failure was that it had been done too late; the patient's health had already deteriorated beyond hope.⁴⁴⁹

In 1902, a proposal "to test an organotherapy for myxoedema in a rational way" suggested transplanting not the whole organ but, as selectively as possible, the parts responsible for internal secretion. The thyroid of new-born animals could be used, it was suggested, because their internal secretion system was especially well developed.⁴⁵⁰ The next year, James Allan, a physician at the Glasgow Royal Infirmary, transplanted the thyroid of a cat, killed especially

⁴⁴⁸ Williams, "Notes on Myxoedema Treated with Extract and Graft of Sheep's Thyroid."

⁴⁴⁹ P. Watson Williams, "Transplantation of Thyroid in Myxoedema," *British Medical Journal* 1 (1903): 580.

⁴⁵⁰ L. W. Ssobolew, "Zur Normalen und Pathologischen Morphologie der Inneren Sekretion," *Virchow's Archiv* 168 (1902): 122–123.

for the purpose, transplanted into a human patient, but the myxoedema did not improve and the patient died two weeks later in a coma. Allan, too, referred to Horsley and Murray in his reports. It was mainly the reports published on thyroid replacement therapy for myxoedema and thyroid transplantation for cretinism, he wrote, that had led him to hope for similar results.⁴⁵¹

Also in Britain, Frederick Charles Pybus (1883–1975) of Newcastle-upon-Tyne tried to transplant human thyroid tissue in 1916. Pybus had done the same thing earlier with adrenal gland tissue in an experimental setting. Because the xenotransplantations of his predecessor Williams had failed, Pybus tried the allogenic approach, i.e. using donor and recipient of the same species, in this case humans. On July 17, 1916, a seriously injured male accident victim was admitted to the hospital where Pybus did his research. Right after the victim's death, the surgeon removed the man's thyroid gland, cut it into three slices, and implanted each slice into the abdominal subcutaneous tissue of two women, thirty-two and thirty-seven years old, both with therapy-resistant myxoedema. None of the transplants worked. At the end of his report, Pybus admitted that although transplants represented the most rational form of therapy, they would continue to fail as long as medical science did not understand the principles involved.⁴⁵²

Pybus' comment shows that by 1916, organ replacement by means of transplantation was regarded as an ideal therapy for the treatment of myxoedema, not least because Murray's organ replacement therapy required the constant and life-long administering of thyroid juice for the affected patient. However, transplantation could unfortunately not be put into practice for the time being. Doctors therefore turned to the older approach of using thyroid

⁴⁵¹ James W. Allan, "Transplantation of the Thyroid Gland," *British Medical Journal* 1 (1903): 268–269; James W. Allan, "Transplantation of the Thyroid Gland in Myxoedema," *British Medical Journal* 1 (1903): 711; James W. Allan, "Transplantation of the Thyroid Gland in Myxoedema, and of the Suprarenal Gland in Addison's Disease," *British Medical Journal* 1 (1903): 764.

⁴⁵² Frederick Charles Pybus, "Notes on Thyroid Grafting," *The Lancet* 2 (1924): 550–551.

extract preparations. The use of thyroid extract, as explained earlier in this chapter, also fit well with Brown-Séquard's organotherapy, which is why Brown-Séquard cited Murray's findings as additional proof for the rational basis of his own approach when he first read about them.⁴⁵³ However, the failure of thyroid grafts in humans still meant that the proof of a direct causal link between the thyroid gland and myxoedema remained unresolved. The subject had not yet been brought to an overall convincing conclusion. The failure of organ therapy with thyroid transplantation not only affected medical practice; it also meant that an important link in the physiological chain of argument was missing.⁴⁵⁴ Typical of the prevailing attitude was a contribution by the Italian doctors Nuno Tiberti and Andrea Franchetti, who, in 1909, repeated Horsley's experiments with thyroid extirpation. They found myxoedematous symptoms in their laboratory animals but could not re-implant the organ. They finally had to content themselves with the statement that, while they thought the anti-myxoedematous influence of the liquefied thyroid gland seemed indisputable, proof of the causal link between the thyroid and myxoedema was still pending.⁴⁵⁵ To provide essential evidence for the causal role of thyroidal secretion in myxoedema, researchers would have to be able to exert complete control over its manifestations. To do so, they needed to remove the necessary cause of the disease in order to prevent it from recurring.

Since this kind of control was still unavailable, the endocrine theory of myxoedema remained debatable. For some, as we have seen before with Eduard Pflüger, myxoedema continued to be a nervous disease; for others, the focus was on the thyroid gland. Up to the 1910s, many specialists thought that thyroidal myxoedema did indeed exist, but that it might be only one

⁴⁵³ Brown-Séquard, "On a New Therapeutic Method Consisting in the Use of Organic Liquids Extracted from Glands and Other Organs," 1146–1147.

⁴⁵⁴ John James R. McLeod, *Myxoedema: Its Pathological Physiology* (London: Arnold, 1913), 88–91.

⁴⁵⁵ Nuno Tiberti and Andrea Franchetti, "Sur les effets de l'extirpation partielle et de l'extirpation totale du thyroïde chez le chien," *Archives italiennes de Biologie* 51 (1909): 127–131.

of many different forms of myxoedema.⁴⁵⁶ One of the problems was that not every patient showed evidence of damage to the thyroid in post-mortem dissection. It therefore seemed that the necessary cause of the disease could not possibly be located in that organ. The correlation between myxoedema and a specific organ lesion was hard to determine anyway: on the one hand, there was hardly any organ that was not pathologically changed in myxoedematous patients; on the other hand, each organ, even in myxoedematous patients, could still sometimes turn out to be healthy.⁴⁵⁷ Consequently, the disease appeared to possess a confusingly wide variety of possible causes. An agreed upon necessary cause that could have served to control the disease was nowhere in sight.

In general, the prospect for both successful thyroid transplantation and a lasting supply of thyroid juice were not good. Although pharmaceutical companies were beginning to manufacture thyroid preparations of animal origins to treat myxoedema, scientific authorities agreed that lasting success was not to be expected.⁴⁵⁸ A “general hopelessness,” as the physician Frederick Allen put it in 1913, had emerged over the whole subject.⁴⁵⁹

Despite all previous failures to determine the exact cause of myxoedema, researchers kept trying to isolate the postulated anti-myxoedematous principle of the thyroid and use it as a remedy to cure myxoedema. In the first two decades of the twentieth century, some of them came quite close to this goal but were unable to convince the medical world of the practicability of their procedures.⁴⁶⁰ In fact, several favourable circumstances had to come together for the “discovery” of thyroxin to occur in 1913 and 1926, including new methods for isolating and yielding increase of thyroid gland extracts, new methods for measuring the

⁴⁵⁶ Joseph H. Pratt, “The Internal Function of the Thyroid,” *Journal of the American Medical Association* 59 (1912): 322–325.

⁴⁵⁷ The same problem has been discussed by Tattersall in relation to the causal determination of diabetes. See: Robert Tattersall, “Pancreatic Organotherapy for Diabetes, 1889-1921,” *Medical History* 39 (1995): 303.

⁴⁵⁸ *Ibid.*, 311–312.

⁴⁵⁹ Allen, *Studies Concerning Myxoedema*, 834.

⁴⁶⁰ Rolleston, *Endocrine Organs*, 86–87.

composition of the blood of patients, and close interdisciplinary cooperation between medical researchers and chemists. Only towards the end of the second decade of the twentieth century did a general consensus about the cause of myxoedema start to emerge. At that time, in 1926, the medical researcher Charles Robert Harrington (1897–1972) of University College London had succeeded in the crystallisation and subsequent synthesis of thyroxin, the thyroid gland's main hormone. Harrington had based his research on the discovery of thyroxin by Edward Calvin Kendall (1886–1972) in 1913.⁴⁶¹ As a result, Murray, who had triggered the search for the anti-myxoedematous principle of the thyroid through his experimental treatment about three decades earlier, was able to present to his students a small bottle of thyroxin in 1929.⁴⁶²

4.9. CONCLUSION

When we look at the details of this discovery, we see how closely the treatment was connected to the overall development of thyroid replacement therapy. Originally, Kendall was tasked with the identification of adverse biochemical compounds that might hinder the acceptance of a donor's thyroid gland in the recipient. The researchers at the Mayo Clinic in Rochester, Minnesota, where Kendall was then working, planned to autotransplant a monkey's thyroid, which they had made atrophic in order to show that the supposed internal secretion was still active. What Kendall found, however, was not an adverse chemical, but the active component of the gland's internal secretion. This step brought the breakthrough

⁴⁶¹ Kendall discovered thyroxin by chance on Christmas Day 1914 when Kendall precipitated crystals of the pure compound from a "white crust" which formed when he had inadvertently fallen asleep in the laboratory while evaporating ethanol from iodothyin, a partially purified extract of hog thyroid gland. However, he was unable to determine its structure, or synthesise it. In the beginning, he was not even sure what exactly he had found on his dish. E.C. Kendall, "The Isolation of a Compound Containing Iodine in the Thyroid," *Journal of the American Medical Association* 64 (1915): 2042–2043; Edward Calvin Kendall and A.E. Osterberg, "The Chemical Identification of Thyroxin," *The Journal of Biological Chemistry* 40 (1919): 265–334; Charles Robert Harrington and George Barger, "Chemistry of Thyroxin: Constitution and Synthesis of Desido-Thyroxin," *Biochemical Journal* 21 (1927): 169–183.

⁴⁶² Rolleston, "Endocrines in Theory and Practice," 1034.

medical practitioners had hoped for. With the successful synthesis of thyroxin by Harington thirteen years later came the direct control over myxoedema by means of one single pharmaceutical compound. Medical science, in conjunction with clinical practice, had finally provided the proof for the endocrine function of the thyroid gland, and myxoedema seemed now curable. In 1930, a standard textbook of medicine stated with certainty that the disease was caused by a deficiency in the secretion of the thyroid gland. The organ disease of myxoedema now had a necessary cause through which it could be controlled.

– CHAPTER 5 –

AT THE INTERFACE OF CLINIC AND UNIVERSITY: THE MEDICAL PROFESSION AND ORGAN REPLACEMENT THERAPY

5.1. INTRODUCTION

So far, I have primarily been concerned with a historical examination of the developing concept of organ replacement therapy related to the thyroid gland. We have seen how the concept emerged from growing tensions between the older disease entities of endemic cretinism and goitre and new observations in Britain that challenged fundamental assumptions about the underlying causes of these conditions as well as their pathology. Over the course of the following two chapters, I will critically examine some larger issues regarding the above developments. In the following chapter, I attribute organ replacement therapy to a particular style of medicine. Here, the specific approach and way of reasoning involved in organ replacement therapy is summed up, characterised, and correlated with the social and professional conditions that made it possible. Besides K. Codell Carter's concept of causal thinking in medicine the following analysis again makes use of John Pickstone's typology of medicine and science as well as some more general remarks on the periodization of clinical medicine during the late nineteenth century. The conjunction of these ideas will provide the framework for an analysis of the changing styles of medical thinking and the emancipation of the medical profession from the subjective, patient-account-centred style of practice to an analytical notion of disease and therapeutics in the (late) nineteenth century.

This change was primarily linked to the rise of university-based research medicine, which began to gather momentum during the second half of the nineteenth century. Thus, related

ideas will be discussed in the second section of this chapter. The rise of a physiological understanding of disease and therapy, which superseded the older anatomical-pathological approach, was a direct consequence of this change and proved to be highly influential in the development of organ replacement therapy.

It should come as no great surprise that this fundamental change in approach did not happen without causing friction and re-evaluation of the role of medicine's (sub-)disciplines, and I will be discussing these issues in relation to the medical practitioners' professional interests at the end of this chapter.

5.2. CHANGING STYLES OF MEDICINE

It was no coincidence that organotherapy and the foundations of a concept regarding the function of the thyroid gland were developed in the late nineteenth century. The underlying disease concepts of cretinism and myxoedema as well as the new therapeutic approach of organ replacement therapy were representative of a very contemporary style of medical thinking and practice. Practitioners of this style were attempting to construct the epistemic base of their knowledge by building upon experimental physiology. This style of medicine arose in the expanding research universities of continental Europe and Britain most of which were associated with improved teaching hospitals and, in a growing number, well-equipped laboratories.⁴⁶³ In the wake of such scientific improvements, this style remained highly influential until the beginning of the twentieth century. The importance of the aforementioned context becomes especially apparent once one considers that the first attempts to elucidate the function of the thyroid gland during the nineteenth century

⁴⁶³ Thomas Neville Bonner, *Becoming a Physician: Medical Education in Britain, France, Germany, and the United States, 1750-1945* (Baltimore: Johns Hopkins University Press, 2000).

remained without much significance.⁴⁶⁴ Evidently, the development of the new concepts depended as much on the existence of certain ideas and observations as on the meaning that contemporary medical practitioners attached to them. This meaning, however, depended on the style of medical thinking that was dominant at that time. The historian of medicine John Pickstone distinguishes between several styles of medicine and scientific thought that emerged at different times, which in turn can then be associated with specific institutional and social contexts. Thus, the different styles can help us to identify the characteristic features of the practical as well as epistemological approaches, by linking together specific ‘ways of knowing’ about what constitutes a scientific method in medicine.⁴⁶⁵

Pickstone holds that, from antiquity to the nineteenth century, the dominant style of medicine was what he calls “biographical medicine.”⁴⁶⁶ This kind of medical practice took place in the context of private consultations—the direct association of an individual physician and a single patient—and was characterised by the individual doctor’s social and economic dependence on the patient being treated. The relationship between doctor and patient was essentially one of patronage.⁴⁶⁷ For the ‘biographical medicine’ of the eighteenth century, for example, the patient’s own account acted as the basis for the doctor’s diagnosis and therapeutic approach.⁴⁶⁸ In Pickstone’s terms, the scientific method associated with this style of medical practice consisted predominantly of the observation and classification of

⁴⁶⁴ Moritz Schiff, for example, did not resume his extirpations of the thyroid gland conducted between 1856 and 1857 until 1883, in the wake of Horsley’s work for the Committee on Myxoedema. Also, it took years for the results of the committee on myxoedema to become influential and applicable in the work of George Murray.

⁴⁶⁵ Pickstone, *Ways of Knowing: a History of Science, Technology and Medicine*. On the different conceptions of scientific methods in the history of medicine see: Warner, “The History of Science and the Sciences of Medicine,” 179.

⁴⁶⁶ Pickstone, *Ways of Knowing: a History of Science, Technology and Medicine*.

⁴⁶⁷ Nicholas D Jewson, “Medical Knowledge and the Patronage System in Eighteenth Century England,” *Sociology* 8 (1974): 371.

⁴⁶⁸ Jewson, “Medical Knowledge and the Patronage System in Eighteenth Century England”; Nicholas D Jewson, “The Disappearance of the Sick Man from Medical Cosmology,” *Sociology* 10 (1976): 225–244.

phenomena according to their observable clinical features.⁴⁶⁹ These practitioners perceived the human body holistically, with all components being intertwined and interconnected through the flows of the bodily humours. Diseases, therefore, did not affect an isolated part of the body but the human being in its entirety. The physician's intervention thus aimed at restoring the body's humoral balance through therapeutic measures or changes in the lifestyle of the patient. Thus, medical interventions were highly individualised measures and more often than not aimed at prophylaxis rather than cure.⁴⁷⁰ Blackie, MacClelland, and the other doctors who investigated cretinism in Britain from an endemic point of view, were examples of this type of medical doctor. With their natural history approach, they investigated cretinism as a disease of the entire human being within the context of specific environmental conditions. To assign this disease its particular position in an overall nosological system they used its observable clinical features.

A different style of medicine emerged in tandem with the rise of large hospitals—*hospital medicine*, as the historians Erwin Ackerknecht and Michel Foucault characterised it, or *analytical medicine* in Pickstone's terms. In the hospital, the aforementioned system of patronage between doctor and patient became reversed. Usually, patients were admitted into a hospital because they were too poor to afford any other kind of medical care. Here, it was the patient who became economically and socially dependent on the doctor.⁴⁷¹ Also,

⁴⁶⁹ John V Pickstone, "Ways of Knowing: Towards a Historical Sociology of Science, Technology and Medicine," *British Journal for the History of Science* 26 (1993): 439–443.

⁴⁷⁰ Russell C. Maulitz, *Morbid Appearances* (Cambridge: Cambridge University Press, 1987), 13–18, 228; Pickstone, "The Biographical and the Analytical: Towards a Historical Model of Science and Practice in Modern Medicine"; Cay-Rüdiger Prüll, "Pathology and Surgery in London and Berlin 1800-1930: Pathological Theory and Clinical Practice," in *Pathology in the 19th and 20th Centuries: The Relationship Between Theory and Practice* (Sheffield: EAHMH Publications, 1998), 71–91.

⁴⁷¹ Pickstone, *Ways of Knowing: a History of Science, Technology and Medicine*, 35–37. In his work on medicine in post-revolutionary Paris, Ackerknecht described the constitution of "hospital medicine," which, in his view, evolved from "hospital bed medicine" and was followed by "laboratory medicine." For a good overview of his ideas see: Erwin H Ackerknecht, *Medicine in the Paris Hospital 1794-1848* (Baltimore: Johns Hopkins University Press, 1966), esp. 40–68. Jewson relates the change to the disappearance of the patronage relationship between doctor and patient: Jewson, "The Disappearance of the Sick Man from Medical Cosmology." And in his now classic account, Foucault discussed the

diagnosis and treatment were no longer determined by the patient's narrative but on the doctor's examination and judgement. The physicians began to employ new techniques of physical examination and used symptoms and signs that appeared on the body's surface to determine the kind of localised lesions present inside of the body. These internal lesions now became prominent to form the basis for the conceptualisation and systematic classification of pathological processes. The patient's idiosyncrasies—including his own illness narrative—played only a minor role here; similar lesions in a group of patients were largely regarded as comparable.⁴⁷²

According to Owsei Temkin, this change of style in medicine was also the point at which the surgical approach to the body and disease became important; especially so, as medical practitioners' views of disease depended on their approach to the body.⁴⁷³ Consequently, the surgeon's view was anatomical; the focus being on structures. In their professional opinion, it was the individual parts of the body that were affected by characteristic disease processes. These localised disease processes then called for corresponding surgical interventions in the affected sites, such as an extirpation of the thyroid gland in goitre. This focus on surgical interventions also contributed to the notion of organ replacement therapy: if a vital organ had been extirpated, any associated function had to be replaced, or at the very least compensated for. Accordingly, the localisation of disease allowed for the appropriate mode of treatment to be performed.⁴⁷⁴ Thus, a surgeon understood the body's structures and function by

subject from a predominantly epistemological perspective: Michel Foucault, *The Birth of the Clinic: An Archaeology of Medical Perception* (Routledge, 2003). For the changes hospital medicine brought to the education of doctors, see: Bonner, *Becoming a Physician: Medical Education in Britain, France, Germany, and the United States, 1750-1945*, 103–141.

⁴⁷² Volker Hess, *Von der Semiotischen zur Diagnostischen Medizin*, vol. 66, *Abhandlungen zur Geschichte der Medizin und der Naturwissenschaften* (Husum: Matthiesen Verlag, 1993), 35–42; Pickstone, "The Biographical and the Analytical: Towards a Historical Model of Science and Practice in Modern Medicine," 31.

⁴⁷³ Temkin, "The Role of Surgery in the Rise of Modern Medical Thought." In principle, this sequence has been confirmed by Maulitz, *Morbid Appearances*; Lesch, *Science and Medicine in France: The Emergence of Experimental Physiology, 1790-1855*.

⁴⁷⁴ Maulitz, *Morbid Appearances*, 12, 227–229.

subdividing it into its components and then analysing them.⁴⁷⁵ Around 1800, physicians increasingly adopted this view to the degree that the two initially separated branches of the medical profession were beginning to merge as ways of looking at things in medicine and surgery converged. For medicine, the outcome was a kind of “surgicalization.”⁴⁷⁶ The criteria that had hitherto served to describe and classify external diseases were now applied to internal diseases as well. The paradigmatic science of medicine was pathological anatomy, which was closely related, conceptually and practically, to surgery.⁴⁷⁷

During the second half of the nineteenth century, this analytical, anatomically oriented approach had led researchers to interpret certain constellations of symptoms as organ based diseases. As described in Chapter 2, William Ord applied this approach to the thyroid gland, which then also formed the base of the Committee’s work and organisation. The method of correlating clinical pictures with post-mortem findings had emerged under the special social conditions of the modern teaching hospital, with its particular differences in the balance of the relationship between doctor and patient and the very large numbers of the latter. Ord worked at Guy’s Hospital in London, a prototype of this new kind of hospital.⁴⁷⁸ Only in such an institution was it possible for him to assemble a number of patients with the same clinical picture in order to document their clinical symptoms and perform autopsies when they died.⁴⁷⁹

⁴⁷⁵ Pickstone, “Ways of Knowing: Towards a Historical Sociology of Science, Technology and Medicine,” 439–443.

⁴⁷⁶ Schlich, *The Origins of Organ Transplantation: Surgery and Laboratory Science, 1880-1930*, 148.

⁴⁷⁷ For the historical positions of surgery and pathological anatomy in France and the United Kingdom, see Maulitz, *Morbid Appearances*.

⁴⁷⁸ Bonner, *Becoming a Physician: Medical Education in Britain, France, Germany, and the United States, 1750-1945*, 49; Hector Charles Cameron, *Mr Guy’s Hospital, 1726-1948* (London: Longmans, Green & Co., 1954), 218–231.

⁴⁷⁹ Leonard G Wilson, “Internal Secretions in Disease: The Historical Relations of Clinical Medicine and Scientific Physiology,” *Journal of the History of Medicine and Allied Sciences* 39 (1984): 264–266.

5.3. LABORATORY MEDICINE AND THE UNIVERSITY SETTING

In hospital medicine, the priority was service: curing patients as well as training aspiring doctors and students. Similarly, anatomical pathology, the science associated with this type of medical practice, was geared towards an immediate service function within hospitals.⁴⁸⁰ With the creation of the modern research-orientated university, the whole orientation of medical science and education began to be transformed. For university medicine, service in the form of patient care was only one concern amongst many. Its representatives, i.e. physicians and surgeons alike, were mostly concerned with creating new knowledge. They were expected to produce this knowledge, not just provide a certain kind of service.⁴⁸¹ This was also the context in which scientific disciplines were established at the university.⁴⁸² These disciplines competed with each other not only for authority but also for material resources. Making knowledge production such a priority was only possible in the institutional context of the new nineteenth-century research universities and teaching hospitals. They formed a framework that enabled medical scientists to pursue an ideal according to which the subject under investigation determined the direction the research would and should take. Medical scientists could therefore choose the appropriate research methods according to the requirements of the subject under investigation, without interference from non-specialists. Furthermore, it was the medical scientists themselves, in their respective disciplines, who chose their very own subjects of interest to be investigated.⁴⁸³

⁴⁸⁰ Maulitz, *Morbid Appearances*, 77; Prüll, "Pathology and Surgery in London and Berlin 1800-1930: Pathological Theory and Clinical Practice," 87.

⁴⁸¹ Bonner, *Becoming a Physician: Medical Education in Britain, France, Germany, and the United States, 1750-1945*, 182–202; Thomas Schlich, "Pathological Theory - Surgical Practice? The Rationale Behind the First Organ Transplantation," in *Pathology in the 19th and 20th Centuries: The Relationship Between Theory and Practice*, ed. Cay-Rüdiger Prüll (Sheffield: EAHMH Publications, 1998), 55–69.

⁴⁸² Donald Stephen Lowell Cardwell, *The Organisation of Science in England* (London: Heinemann, 1972).

⁴⁸³ Pickstone, *Ways of Knowing: a History of Science, Technology and Medicine*, 143–145; Bonner, *Becoming a Physician: Medical Education in Britain, France, Germany, and the United States, 1750-1945*; Fagot-Largeault, "On Medicine's Scientificity: Did Medicine's Accession to Scientific 'Positivism' in the Course of the Nineteenth Century Require Giving up Causal (Etiological) Explanation?," 108.

Under these conditions, the control of natural phenomena became the scientific method of choice, a method linked closely to the laboratory, a place set up for the express purpose of the optimal control over natural phenomena by scientists.⁴⁸⁴ Accordingly, the rise of laboratory science was an important factor in the development of university science in the late nineteenth century: the expansion of the European universities between 1870 and 1914 resulted largely from the growth of the experimental laboratory sciences, especially experimental chemistry, physiology, and physics.⁴⁸⁵ Expensive laboratories and institutes were set up for scientists, who were exempt from other activities and duties so that they could pursue their experiments in these new settings.⁴⁸⁶ At the same time, laboratory science also became the new conceptual basis of modern medicine and ultimately shaped knowledge about the human body in a specific way.⁴⁸⁷ Disciplines not directly concerned with patient care, such as pathology and physiology, were now seen as basic sciences; that is, they were expected to give clinical medicine its scientific foundation.⁴⁸⁸ This style of medicine largely corresponds to what Pickstone calls *experimental medicine*.⁴⁸⁹

With this experimental style of medicine, the applied scientific method no longer consisted of observation and classification as in the clinical—Pickstone's *biographical medicine*—and pathologically orientated styles of medicine. Scientific research now amounted to controlling those phenomena that previous styles sought only to prevent or fight, through active intervention. In order to investigate the functions of the body, researchers in the laboratory used surgical intervention to selectively change the conditions under which the processes of

⁴⁸⁴ Cunningham and Williams, *The Laboratory Revolution in Medicine*.

⁴⁸⁵ Pickstone, "Objects and Objectives: Notes on the Material Cultures of Medicine"; Cardwell, *The Organisation of Science in England*, 101–105.

⁴⁸⁶ Schlich, *The Origins of Organ Transplantation: Surgery and Laboratory Science, 1880-1930*, 211.

⁴⁸⁷ Pickstone, "Ways of Knowing: Towards a Historical Sociology of Science, Technology and Medicine," 449–452; Terrie M Romano, *Making Medicine Scientific: John Burdon Sanderson and the Culture of Victorian Science* (Baltimore: Johns Hopkins University Press, 2002), 75–92.

⁴⁸⁸ Bynum, "'C'est Un Malade': Animal Models and Concepts of Human Disease," 398.

⁴⁸⁹ Pickstone, *Ways of Knowing: a History of Science, Technology and Medicine*; Pickstone, "Ways of Knowing: Towards a Historical Sociology of Science, Technology and Medicine"; Pickstone, "Objects and Objectives: Notes on the Material Cultures of Medicine."

life and disease occurred, and then registered their reaction with the help of physical and chemical measurement methods.⁴⁹⁰ In this context, understanding a biological phenomenon was equivalent to being able to cause and prevent it at will. Knowledge and the ability to control life phenomena had become one and the same thing.⁴⁹¹ Extending the knowledge and results gained in the laboratory to the profession outside it was to apply complete control over diseases, or so the idea went.⁴⁹² The break that experimental medicine made with previous concepts of medicine consisted of its explicit programme to willingly control the phenomena of life.⁴⁹³ Paradigmatic for this approach is Claude Bernard's *Introduction to the Study of Experimental Medicine*, published in 1865.⁴⁹⁴ Bernard wanted to extend the control over nature which had been attained by chemistry and physics to the complex world of biological phenomena, including, of course, medicine. Through meticulous animal experiments, in which only one factor was changed at a time, the new breed of researchers could extend their control, as he claimed, to include even those phenomena that had so far been regarded as individual, idiosyncratic and utterly unpredictable. Since a process that can be controlled in the laboratory animal should in principle also be controllable in patients, the future of medicine lay in extending the power of experimental physiology to the field of therapy and prophylaxis.⁴⁹⁵ Experimental physiology arose from this very model in the nineteenth century. Bernard's *Introduction* became something of a manifesto for the new field's identity but also a polemic against the primacy of clinical medicine and its

⁴⁹⁰ Lesch, *Science and Medicine in France: The Emergence of Experimental Physiology, 1790-1855*, 12–13, 80–100.

⁴⁹¹ Temkin, "The Scientific Approach to Disease: Specific Entity and Individual Sickness."

⁴⁹² Christoph Gradmann, *Krankheit im Labor: Robert Koch und die medizinische Bakteriologie* (Göttingen: Wallstein, 2005).

⁴⁹³ Lesch, *Science and Medicine in France: The Emergence of Experimental Physiology, 1790-1855*, 199.

⁴⁹⁴ Bernard, *An Introduction to the Study of Experimental Medicine*.

⁴⁹⁵ Pickstone, "Objects and Objectives: Notes on the Material Cultures of Medicine," 16.

concentration on clinical observation, pathological anatomy, and statistics, in favour of abstraction, generalisation, and science.⁴⁹⁶

Just as in the earlier case of pathological anatomy earlier, experimental physiology was initially linked to surgery, in its development as well as its approach.⁴⁹⁷ As Horsley emphasised repeatedly, the success of experimental physiology was a result of new surgical techniques that made the internal organs accessible to the observer and enabled him to manipulate their function.⁴⁹⁸ Even though physiologists naturally operated on animals, not on humans, they essentially applied the same fundamental principles as surgeons.⁴⁹⁹

In the context of university medicine, the discipline of physiology competed with other disciplines for intellectual authority and economic resources. Physiologists laid claim to the role of experts in elucidating the organism's normal and pathological functions. Thus, when surgeons like Jean-Jacques Reverdin and Theodor Kocher noticed the surprising consequences of thyroid removal, both Victor Horsley in Britain as well as Moritz Schiff in Germany took this event as an opportunity to emphasise physiology's claim to leadership. They warned clinicians to get the physiologist's opinion *before* trying out a therapy of this kind. In a similar way, the conflict between the British physiologists opposing Brown-Sequard's notion of internal secretion and the physician George Murray regarding the organ replacement concept in connection with myxoedema should be understood in the context of such interdisciplinary competition.⁵⁰⁰

⁴⁹⁶ Lesch, *Science and Medicine in France: The Emergence of Experimental Physiology, 1790-1855*, 1–30, 99–100, 199–200.

⁴⁹⁷ Cunningham and Williams, *The Laboratory Revolution in Medicine*, 14–71.

⁴⁹⁸ Horsley, "Some Researches Carried Out During the Last Ten Years into the Functions of the Brain and the Thyroid Gland."

⁴⁹⁹ Maulitz, *Morbid Appearances*, 95–102; Coleman, "The Cognitive Basis of the Discipline: Claude Bernard on Physiology," 52–53.

⁵⁰⁰ Schlich, "Changing Disease Identities"; Borell, "Organotherapy, British Physiology, and Discovery of the Internal Secretions"; Wilson, "Internal Secretions in Disease: The Historical Relations of Clinical Medicine and Scientific Physiology."

5.4. THE RISE OF SURGERY IN BRITAIN AND ITS IMPORTANCE FOR THE CHANGING CONCEPT OF DISEASE

The new style of medicine with its focus on experimental physiology also reshaped surgery and with it the understanding of disease in Britain. We can distinguish between several ideal styles of surgery in Britain according to their respective scientific orientation. Firstly, the *local/anatomical* style of surgery was based on pathological anatomy, and its approach to treatment was the extirpation of diseased body structures. Secondly, the subsequent, *functional/physiological* style of surgery was focussed on physiology, developing methods of restoring the functions of the body. Lastly, the *systemic* style of surgery typically aimed at the replacement of biological functions, an aim commonly pursued by interdisciplinary collaboration.⁵⁰¹ The transition from the *local/anatomical* style to the *physiological/functional* essentially corresponds to the change from *analytical* to *experimental* medicine in Pickstone's typology.⁵⁰²

Within the context of the first style, surgery experienced an unprecedented expansion. Surgery's formula for success until the 1880s was to cut out the diseased part of the body, the extirpation of goitres being a typical instance of this style of surgery. Victor Horsley is a perfect example of this type of surgeon. Horsley began to experiment with total thyroidectomies in animals at around the same time as Kocher performed his human thyroidectomies. Horsley propagated total thyroidectomies in monkeys, and thus became the first researcher to successfully (re-)create the thyroid insufficiency syndrome in animals.⁵⁰³ Like Kocher's *cachexia strumipriva* in the Swiss-German context, Horsley's experiments

⁵⁰¹ See: Ulrich Tröhler, "Surgery (Modern)," in *Companion Encyclopaedia of the History of Medicine*, vol. 2 (London: Routledge, 1993), 984–1028. Tröhler, however, calls these "periods." However, I prefer to call them styles so as to water down the otherwise quite strong link to certain periods of time.

⁵⁰² Pickstone, *Ways of Knowing: a History of Science, Technology and Medicine*.

⁵⁰³ As we have seen before, Schiff and other scientists used dogs as their laboratory animal of choice. However, dogs, as all carnivores, rely heavily on the thyroid for their metabolism and thus died within hours after the operation without ever developing any deficiency symptoms.

yielded results that later served as an argument in favour of the organ replacement concept. In conjunction with his surgical education, Horsley had trained in the physiological laboratory of John Burdon Sanderson and Edward Schäfer at University College London from 1873 to 1878. He was thus exemplary well positioned within the new physiologically orientated style of medicine. Horsley's student George Murray later wrote of these early experiments that it was the "ignorant intervention of surgeons [like Horsley], through which the harmony of biological interrelations are revealed."⁵⁰⁴ That he, of all people should make this statement proves the point that the change from organ removal—on the lines of the early experiments of Schiff and others—along the organ replacement concept and therapy was accompanied by a generational change in the disciplines of surgeons, physicians, and physiologists alike. In his practice, Murray explored the organotherapeutic substitution of the function of the same organ in humans that his teacher Horsley successfully removed in animals.

The invention of organ replacement therapy was thus part of the transition from *localised* to *physiological* surgery. In the 1880s, the old surgery rose to hitherto unattained heights of technical perfection and extended its field of application to ever more body parts. In quite a few domains, however, as in the case of goitre, the limits of usefulness of this style of surgery had been reached. Now that total organ extirpations were technically possible, the functional consequences of an absent organ became evident. Kocher's *cachexia strumipriva* comes chronologically first and is also typical. The consequences of excessive extirpation actually forced medical doctors to take a new course and to try and create the opposite effect by replacing the organ's function in the body.⁵⁰⁵

Horsley's response in fact followed very much the traditional surgical rationale of repairing damaged body structures. His first explanations of the after-effects of thyroidectomy also

⁵⁰⁴ Horsley, "Note on a Possible Means," 288.

⁵⁰⁵ Michael J. Aminoff, *Brown-Séquard: An Impossible Genius Who Transformed Medicine* (Oxford: Oxford University Press, 2011), 153.

followed a surgical logic. He attributed these to a localised and purely mechanical influence on the circulation of the blood or respiration, and therefore tried to reconstruct local anatomical conditions, thereby quasi reversing the extirpation.⁵⁰⁶ At this point, Horsley was still firmly grounded in the familiar style of the traditional surgical approach. Once surgeons switched to a new interpretation of organ replacement and started seeing it as the replacement of a specific function, however, they also switched to a new surgical approach.⁵⁰⁷ The new kind of organ replacement therapy no longer followed a localised strategy; the functions of thyroid tissue could be replaced by mimicking the action of the gland through the administration of extracts gained from the gland itself. Even though these new strategies evolved at the intersection of internal medicine and surgery, the new interpretative framework gave these strategies a new meaning. They were no longer reparative but amounted to deliberations into complex internal functions of the body.⁵⁰⁸

It is no coincidence that the organ replacement therapy concept began with the thyroid. In terms of function, the thyroid gland is an internal organ; topographically, however, it is on the body's surface, visible and accessible to surgical manipulation as well as the physician's touch. Another important organ for the development of the organ replacement concept was the testicle; yet another example of a superficially located internal organ. Testicles were relatively easy to remove, and the consequences that could be observed after castration gave Brown-Séquard the idea for developing his ideas of internal secretion and the resulting therapeutic approach of organotherapy.⁵⁰⁹

⁵⁰⁶ Horsley, "Some Researches Carried Out During the Last Ten Years into the Functions of the Brain and the Thyroid Gland."

⁵⁰⁷ Schlich, *The Origins of Organ Transplantation: Surgery and Laboratory Science, 1880-1930*, 193–206.

⁵⁰⁸ Borell, "Organotherapy, British Physiology, and Discovery of the Internal Secretions"; Borell, "Origins of the Hormone Concept."

⁵⁰⁹ Borell, "Origins of the Hormone Concept"; Aminoff, *Brown-Séquard: An Impossible Genius Who Transformed Medicine*.

Concurrent with the transition from anatomically orientated surgery to the physiological style of surgery, surgeons shifted the focus of their interests from structure to function. However, this change was not limited to surgery alone. Another manifestation was the rise of physiology, which now superseded anatomical pathology as the most important basic science of medicine. Clinical disciplines, including surgery and internal medicine, became more physiologically orientated, as did the theoretical disciplines. Even the field of pathology itself participated in this general re-organisation.⁵¹⁰ Pathologists became engaged in experimental pathology and started using animal models in the same way as physiologists did. The new generation of researchers interested in functional physiology could no longer relate to the observational, anatomically orientated approach of their predecessors. Thus, in 1892, Victor Horsley wondered about the earlier, purely anatomically oriented research on the thyroid—which ironically included his own observations from ten years before. To him, it was now obvious that an approach that tried to explain the function of an organ on the basis of its structural details was bound to fail. Horsley saw experimentation as “the only true method of inquiry.”⁵¹¹ It puzzled him how much had been written and argued about the thyroid gland without any of the authors having tested their hypotheses with a simple experiment.⁵¹² For this reason, the thyroid gland had only been linked to specific diseases through the physiological approach in the first place.

Organ replacement therapy did not aim for the reconstruction of original anatomical conditions either; it was concerned with the replacement of the organ’s *function*.⁵¹³ While the morphological approach had still provided the theoretical basis for the previous generation of

⁵¹⁰ Prüll, “Pathology and Surgery in London and Berlin 1800-1930: Pathological Theory and Clinical Practice.”

⁵¹¹ Horsley, “Remarks on the Function of the Thyroid Gland: a Critical and Historical Review,” 216.

⁵¹² Horsley, “On the Function of the Thyroid Gland,” 6; Horsley, “Remarks on the Function of the Thyroid Gland: a Critical and Historical Review,” 216.

⁵¹³ Biedl, *The Internal Secretory Organs: Their Physiology and Pathology*, 372; Ivo Geikie Cobb, *The Organs of Internal Secretion, Their Diseases and Therapeutic Application: A Book for General Practitioners* (London: Baillière, Tindall and Cox, 1921), 132–133; Harrower, *Outlines of Organotherapy*, 22.

surgeons and physicians, pathological anatomy merely played the role of an auxiliary science in the physiological approach of organ replacement therapy. Pathologist's services were used for determining whether a condition had been there in the first place, e.g. by performing a post-mortem examination. But even on this issue they did not always have the last word. As surgeons and physicians were beginning to be concerned with functional rather than anatomical success, they preferred to trust their own clinical judgements instead of pathologists' diagnoses in conflicting or unclear situations, thus re-emphasising the old power hierarchy in medicine, in which the doctor attending the patient was also the one who had the final say about the diagnosis.⁵¹⁴ Nobody wanted to have a functionally favourable outcome spoiled by negative morphological findings. "It is not right," a physician wrote in an article surveying the recent developments in thyroid replacement therapy in 1898, "to doubt clinical success on the basis of unfavourable histological findings alone."⁵¹⁵

5.5. FROM THE LABORATORY TO THE CLINIC AND *VICE VERSA*

Thus far, we have seen that during the late nineteenth century, surgery established itself alongside internal medicine as a scientific research discipline at the university. As in most other disciplines, surgeons and physicians now began to define their professional goals according to their own priorities and began looking towards the experimental laboratory sciences for their standard of scientific respectability. This was the case especially for university surgeons because only scientific respectability guaranteed a positive status of their field and its practitioners.⁵¹⁶ Accordingly, innovative surgeons took laboratory science as their

⁵¹⁴ For this point see: Lawrence, "Democratic, Divine, and Heroic: The History and Historiography of Surgery," 33.

⁵¹⁵ Beadles, "The Treatment of Myxoedema and Cretinism, Being a Review of the Treatment of These Diseases with the Thyroid Gland, with a Table of 100 Published Cases," 533.

⁵¹⁶ Horsley in Britain and Kocher in Switzerland emphasised this point over and over again; see: Horsley, "Experimental and Clinical Contributions of Thyroid Tissue Replacement," 154; Horsley, "Some Researches Carried Out During the Last Ten Years into the Functions of the Brain and the Thyroid

main point of reference and started applying the principles of physiology.⁵¹⁷ Thus, practitioners who applied the emerging organ replacement therapies, often also conducted animal experiments.⁵¹⁸ The investigation of organ replacement therapy was therefore an area where surgery, internal medicine, and the laboratory sciences coincided, physiological laboratories in general played a central role in establishing organ replacement therapy as a medical concept. It was this connection to the laboratory that enabled organ replacement therapy to emerge as a generally acknowledged, viable, and scientifically valid procedure.⁵¹⁹ In fact, the first phase of organ replacement therapy from 1880 to 1903 is an impressive example of the extent to which scientific medicine legitimised itself through the laboratory sciences.⁵²⁰

The decisive impetus for the implementation of the concept of organ replacement therapy in connection with thyroid disorders came from Victor Horsley's laboratory. Horsley was a typical example in that he tried to base his clinical practices on physics and physiology. He had trained at University College London, one of the most important, if not the most important centres of a scientifically orientated style of medicine in Britain. His articles were published in the *British Medical Journal*, *The Proceedings of the Royal Society*, *The Lancet*, *Brain*, and other journals which were the major venue of publication for this type of medical research at the time. Even though Horsley worked mostly as an experimental physiologist, it was his

Gland"; Kocher, "Über die Bedingungen erfolgreicher Schilddrüsenimplantation beim Menschen," 532–533.

⁵¹⁷ On this point see: Bynum, *Science and the Practice of Medicine in the Nineteenth Century*, 222; Lawrence, "Democratic, Divine, and Heroic: The History and Historiography of Surgery."

⁵¹⁸ See the discussion in Chapter 3.

⁵¹⁹ The scientific validation of organ replacement therapy occurred in tandem with endocrinology. For this, see the articles of Merriley Borell: Borell, "Organotherapy, British Physiology, and Discovery of the Internal Secretions"; M. Borell, "Setting the Standards for a New Science: Edward Schäfer and Endocrinology," *Medical History* 22, no. 3 (1978): 282–290; Merriley Elaine Borell, "Brown-Sequard's Organotherapy and Its Appearance in America at the End of the Nineteenth Century," *Bulletin of the History of Medicine* 50 (1976): 309–320.

⁵²⁰ For a good survey, see: Bynum, *Science and the Practice of Medicine in the Nineteenth Century*.

extraordinary surgical skill that allowed him to induce supposedly myxoedematous symptoms in laboratory animals.⁵²¹

Although the disciplines of university medicine competed with each other, they were however not strictly separate in content and method or even, on occasion, in their practitioners.⁵²² Physicians, surgeons, and physiologists, sometimes collaborated with each other. In Britain, physiology became a particularly attractive discipline to team up with. The field had become thoroughly established in terms of institution, concept, and discipline in the course of what has sometimes been called the “second wave” of foundations of new physiological chairs and institutes from the 1870s to the 1890s.⁵²³ The physician George Redmayne Murray, for example, gained his degree in internal medicine and physiology in the late 1880s with the experiments he carried out at the Brown Institution of University College London, the research laboratory focussed on animal experimentation over which Horsley presided. Murray’s training and career are a prime example of the new physiological orientation of medicine at the time, and Murray himself had characterised the physician’s interest in physiological experiments in 1891 as a new phenomenon.⁵²⁴

Horsley emerged as the leading advocate of the organ replacement concept, switching fields several times from surgery to experimental physiology and back again.⁵²⁵ In so doing, he developed the ability to translate clinical problems into a form that experimental physiology

⁵²¹ For Horsley, see: Paget, *Sir Victor Horsley*. No major literature exists on William Dobinson Halliburton, but a starting point can be found in: Neil Morgan, “William Dobinson Halliburton, F.R.S. (1860-1931): Pioneer of British Biochemistry?,” *Notes and Records of the Royal Society of London* 38 (1983): 129–145.

⁵²² Borell, “Organotherapy, British Physiology, and Discovery of the Internal Secretions,” 242–251.

⁵²³ Romano, *Making Medicine Scientific: John Burdon Sanderson and the Culture of Victorian Science*; Bonner, *Becoming a Physician: Medical Education in Britain, France, Germany, and the United States, 1750-1945*; Charles E Rosenberg, “Disease in History: Frames and Framers,” *The Milbank Quarterly* 67 (1989): 1–15; Schiller, “Physiology’s Struggle for Independence in the First Half of the Nineteenth Century.”

⁵²⁴ George Redmayne Murray, *Illustrations of the Inductive Method in Medicine* (London: H.K. Lewis, 1891), 117.

⁵²⁵ Paget, *Sir Victor Horsley*.

could deal with.⁵²⁶ Horsley began his thyroid experiments in 1883 not at one of the traditional teaching hospitals in London but in a university environment after the continental model. In keeping with the typological differentiation between university and hospital medicine, the non-academic teaching hospitals had developed the clinical pathological approach earlier in the nineteenth century, but they were not very interested in experimental research and its corresponding scientific approach.⁵²⁷

5.6. CONTROLLING DISEASE

The invention of organ replacement therapy in the context of experimentally orientated medicine was based on a specific logic. As discussed above, the point was to show that the absence of a particular organ constituted the necessary cause of a particular disease. Controlling this cause would allow control over the corresponding disease.

Organ replacement thus forms part of the more general approach to disease that was emerging at that time. K. Codell Carter has described the focus on the necessary cause of disease as a characteristic feature of modern Western medicine since the second half of the nineteenth century.⁵²⁸ Besides physiology, bacteriology, above all, served as the model for research in many other fields. From dietetics to psychiatry, scientists now defined necessary causes of disease, the control of which would give them control over particular diseases.⁵²⁹ As we have seen in Chapter 1, Kocher, for instance, had pointed out that his predecessors took multiple non-necessary causes into consideration, while he himself preferred to concentrate on the necessary causes as the decisive point for controlling a disease. In 1891, Murray expressly indicated that the lack of thyroid function was the necessary cause of myxoedema.

⁵²⁶ Borell, "Origins of the Hormone Concept," 69.

⁵²⁷ Lawrence, "Incommunicable Knowledge: Science, Technology and the Clinical Art in Britain, 1850-1914."

⁵²⁸ Carter, *The Rise of Causal Concepts of Disease: Case Histories*; Carter, "The Development of Pasteur's Concept of Disease Causation and the Emergence of Specific Causes in Nineteenth-Century Medicine"; Carter, "Ignaz Semmelweis, Carl Mayrhofer, and the Rise of Germ Theory."

⁵²⁹ Carter, *The Rise of Causal Concepts of Disease: Case Histories*; Latour, *The Pasteurization of France*.

He contrasted the powerlessness that had prevailed before with the new power that resulted from knowing and isolating the necessary cause of the disease. And Horsley explicitly compared the degree of control resulting from the mastery over the necessary cause to the control of biological processes in the laboratory. He emphasised that the total surgical extirpation of the thyroid gland would cause the typical syndrome “with the reliability of an experiment.”⁵³⁰ Likewise, Murray pointed out that treatment with thyroid preparations would eliminate the clinical manifestations of thyroid insufficiency “with the reliability of a physiological experiment.”⁵³¹ According to Horsley, the control over the cause of disease led to “sure results” with a certainty “that can be attained with no other therapy anywhere near as rapidly and completely.”⁵³² Because organ replacement therapy eliminated the cause of a disease it was also considered a “causal therapy.”⁵³³ Physiology, with its control over bodily functions, was the explicit model; only “physiological therapy” would bring about “real cures.”⁵³⁴ The patient’s disease was thus to be controlled as perfectly as the biological phenomena of experimental animals in the physiological laboratory; hence Rolleston pointed out in 1936 that thyroid replacement therapy in humans had been carried out “by analogy to animal experiments.”⁵³⁵

Although the correction of organ failure proved to be decisive for the control of disease, organ failure itself was not considered the only cause of disease, because organ failure must, in turn, have a cause of its own. If this earlier link in the causal chain was not eliminated, attempts at organ replacement would prove to be only of temporary value or may even fall prey to the original cause. In practice, however, it was obvious that replacement therapy did

⁵³⁰ Horsley, “Note on a Possible Means.”

⁵³¹ Murray, “Murray 1891 – Note on the Treatment.”

⁵³² Horsley, “Note on a Possible Means.”

⁵³³ George Redmayne Murray, “An Address on the Signs of Early Disease of the Thyroid Gland,” *British Medical Journal* 1 (1909); Doyle, “Myxoedema.”

⁵³⁴ Theodor Kocher, “Concerning Pathological Manifestations in Low-grade Thyroid Diseases,” in *Nobel Lectures: Physiology or Medicine, 1901-1921* (Amsterdam: Elsevier, 1967), 334–335.

⁵³⁵ Rolleston, *Endocrine Organs*, 133.

indeed eliminate the symptoms of organ insufficiency. Moreover, those earlier links in the causal chain of events could not be controlled anyway. Therefore even those doctors who were aware of the fact that thyroid replacement therapy did not affect the underlying disease causation still recommended the procedure.⁵³⁶

This account makes it clear that the concept of organ replacement and the accompanying therapy was not necessarily based on the medical problems to which they were applied. It was only within the framework of experimental and mostly physiologically orientated medicine that medical problems could be conceptualised in the very specific way that made organ replacement procedures conceivable, viable, and desirable. The new concept of organ replacement served to explain existing disease entities, which were established either according to the observable effects of organ removal on the one hand—as with Kocher's *cachexia strumipriva*—or due to the mystifying effects of suspected organ failure—as with the emerging concept of myxoedema in Britain.⁵³⁷ Thus, organ replacement could only become and remain successful if it was associated with an appropriate disease entity. Hence, the question of diagnosis featured prominently in medical articles published on this subject. The correct diagnosis of myxoedema was one of the main points of dispute in the debate on the utility of thyroid gland substitutions.⁵³⁸ In this context, as we have seen before, cretinism had to be differentiated from other forms of infantile mental deficiencies.⁵³⁹ In 1900 Murray

⁵³⁶ Gimlette, *Myxoedema*.

⁵³⁷ Thomas Schlich argues that the developments in the Swiss context of *cachexia strumipriva* gave rise to a larger number of *cachexias*, depending on which organ had been removed, e.g. *cachexia parathyreopriva* for removal of the parathyroid gland, and *cachexia ovaripriva* for the removal of the ovaries, etc. See: Schlich, *The Origins of Organ Transplantation: Surgery and Laboratory Science, 1880-1930*, 59–64, 85–98.

⁵³⁸ Beadles, "The Treatment of Myxoedema and Cretinism, Being a Review of the Treatment of These Diseases with the Thyroid Gland, with a Table of 100 Published Cases"; H.W.G. Mackenzie, "A Case of Myxoedema Treated with Great Benefit by Feeding with Fresh Thyroid Glands," *British Medical Journal* (1892): 940–941.

⁵³⁹ Beadles, "The Treatment of Myxoedema and Cretinism, Being a Review of the Treatment of These Diseases with the Thyroid Gland, with a Table of 100 Published Cases"; *British Medical Journal*, "Myxoedema and Cretinism"; G. Gordon Campbell, "A Case of Sporadic Cretinism," *Montreal Medical*

attributed the large number of failed organotherapeutic thyroid replacements to diagnostic errors. He recommended making the diagnosis “*ex juvantibus*,” i.e. based on the effects of therapy.⁵⁴⁰ Only when therapy with thyroid preparations was tried and shown to have some observable effect, he claimed, could the diagnosis of thyroid insufficiency—myxoedema—be made with any degree of certainty.⁵⁴¹ In one extreme case, this approach was taken even further. In order to avoid the problem of misdiagnosis, the surgeon John Logan at Guy’s Hospital in 1916 limited the indication of thyroid gland failure to ‘surgical’ thyroid diseases, i.e. technically *cachexia strumipriva*, rather than thyroid failure caused by any other means. Under the heading of ‘surgical’ Logan simply included all diseases which he thought could be cured by thyroid replacement therapy.⁵⁴²

The strategy of constructing disease entities according to their necessary cause was also common in other areas. Murray himself referred to bacteriology, the most important parallel example, when he explained how such a broad range of different disease symptoms could be connected to insufficient thyroid function. Bacteriology had demonstrated that even extremely diverse clinical pictures could have the same cause, since clinical differences stemmed from differences in quantity of the same infectious agent.⁵⁴³ Furthermore, he compared the diagnosis of thyroid deficiency *ex juvantibus* with the same procedure in the diagnosis of syphilis.⁵⁴⁴

As the construction of disease entities shows, different methods of knowledge production resulted in different views of the body, of disease, and of the doctor’s role in treating those

Journal (1899): 1899; Parker et al., “Parker, Telford-Smith et Al. 1896 – A Discussion on Sporadic Cretinism.”

⁵⁴⁰ George Redmayne Murray, *Diseases of the Thyroid Gland: Myxoedema and Cretinism* (London: H.K. Lewis, 1900), 34–37.

⁵⁴¹ *Ibid.*, 115.

⁵⁴² Logan, “Surgical Thyroid Disease.”

⁵⁴³ George Redmayne Murray, “Bacteriology and the Medical Curriculum,” *British Medical Journal* no. 2 (1896): 906.

⁵⁴⁴ George Redmayne Murray, “Some Advances in General and Preventive Medicine Due to Comparative Pathology,” *The Lancet* no. 1 (1894): 730–733.

diseases. In turn, theories of disease causation were determined by the mode of knowledge production. McClelland, Blackie, and others, who collected their data in rural areas, for example, came up with complex, multifactorial causation theories. Curling, Fagge, Gull, and Ord, who combined observations with findings at autopsies, arrived at the view that the disease should be characterised by the respective localised pathological changes within the body. The functional organ replacement concept, too, corresponded to specific methods of knowledge production. It was the active intervention of surgeons and physiologists and their interest in controlling complex life processes through local manipulations that led to the invention of organ replacement therapy.

5.7. THE ORGAN REPLACEMENT CONCEPT AND COMPETING THEORIES

As with most other medical discoveries, the concept of internal secretions and the resulting idea of Murray's replacement therapy by means of liquefied thyroid glands were not accepted right away. The controversy that flared up between Murray and Horsley on the one hand and the German physiologist Eduard Pflüger on the other hand about the organ replacement principle in myxoedema provides us with the opportunity to follow the progress of scientific controversy typical for university based medicine of the late nineteenth and early twentieth centuries.⁵⁴⁵

The physiologist Eduard Pflüger of Bonn, who was already in his seventies by the time he argued against the findings of Murray and Horsley, was the most prominent and influential opponent of the new organ-centred conception of myxoedema;⁵⁴⁶ as mentioned before, his

⁵⁴⁵ Ugo Lombroso, "Die Gewebelemente, welche die innere Sekretion besorgen," *Ergebnisse der Physiologie* 9 (1910): 11–12. We briefly have encountered Pflüger before in Chapter 3.

⁵⁴⁶ In addition to myxoedema, Pflüger was also an avid opponent of the organ-centred concept of diabetes; see: Thomas Schlich, "Making Mistakes in Science: Eduard Pflüger, His Scientific and Professional Concept of Physiology, and His Unsuccessful Theory of Diabetes," *Studies in History and Philosophy of Science* 23 (1993): 411–441.

own myxoedema theory, like most theories before Murray and Horsley, focussed on the nervous system. Pflüger first commented on the internal secretion approach to myxoedema in 1903. He integrated his observations within the older neural theory that had long been propagated by physiologists and regarded the thyroid's internal secretion—if it existed at all—as a kind of appendage to the neural networks responsible for maintaining a healthy body. Along these lines, the nervous system would use the internal secretion of the thyroid as one way to carry out its regulatory function. The disruption of this mechanism would therefore be only one of many possible causes of myxoedema, meaning that organ failure of the thyroid was not a necessary cause of the disease.⁵⁴⁷ To Pflüger, even the transplant experiments of Horsley left ample room for divergent interpretations.⁵⁴⁸

In 1905, Pflüger, who was evidently under the impression that his critical ideas were not being taken seriously enough, proceeded to perform his own experiments.⁵⁴⁹ Because thyroidectomies were a difficult operation to perform, he hired the Bonn surgeon Oscar Witzel for the technical execution of the procedure. The outcome was exactly the same as in previous experiments: Pflüger and Witzel used dogs as their experimental subjects, and all their dogs died after total thyroidectomy, exhibiting massive tetanic seizures. But Pflüger also reported a new observation: dogs whose thyroids had only been partially removed exhibited the typical myxoedematous symptoms of lethargy, increase in body mass, incoordination, etc., while those that had undergone radical extirpations exhibited none, or only traces, of

⁵⁴⁷ Eduard Pflüger, "Abwehr Gegen Meine Kritiker," *Pflüger's Archiv Für Die Gesamte Physiologie Des Menschen Und Der Thiere* 110 (1903): 1–120.

⁵⁴⁸ Pflüger derived this argument from his studies on diabetes mellitus; see: Eduard Pflüger, "Über die im tierischen Körper sich vollziehende Bildung von Zucker aus Eiweiß und Fett: Zur Lehre vom Diabetes mellitus," *Pflüger's Archiv* 106 (1904): 1–66.

⁵⁴⁹ Eduard Pflüger, "Die Bedeutung der Neuesten Arbeiten über die Interne Sekretion: Vorläufige Mitteilungen," *Pflüger's Archiv für die gesamte Physiologie des Menschen und der Thiere* 106 (1905): 168–172; Eduard Pflüger, "Ob die Totalexstirpation der Schilddrüse mit Notwendigkeit das Myxoedem Bedingt," *Pflüger's Archiv für die gesamte Physiologie des Menschen und der Thiere* 106 (1905): 181–188. Pflüger also drew parallels to his studies on diabetes mellitus. For this, see: Eduard Pflüger, "Ein Beitrag zur Frage des im Pankreasdiabetes ausgeschiedenen Zuckers," *Pflüger's Archiv für die gesamte Physiologie des Menschen und der Thiere* 108 (1905): 115–188; Eduard Pflüger, *Das Glykogen und seine Beziehungen zur Zuckerkrankheit*, 2nd ed. (Bonn: Hager, 1905).

these additional symptoms. These results led Pflüger to conclude that, as the total removal of the thyroid gland was succeeded only by tetany and not the typical symptoms of myxoedema, myxoedema had nothing at all to do with the lack of thyroid tissue. Pflüger therefore claimed that Horsley's experimental extirpations had not been total and should therefore not be trusted, but also that Murray's patients were not affected by a loss of thyroid tissue, or, if at all, that this loss had nothing to do with their myxoedematous condition. The German physiologist now warned all researchers not to lay their foundations on results so obviously obtained by incorrect techniques and faulty conclusions.

Thus attacked, Horsley defended his work,⁵⁵⁰ by insisting on the correctness of his surgical technique, stating that it was identical to the one used by Witzel. He then left the common ground of experimental physiological procedures and emphasised, in defence of his own and Murray's results, the unsuitability of dogs as experimental subjects for thyroid extirpation studies. He stated his surprise that Pflüger, being a straight physiologist, had not known that dogs, as well as all other carnivores, always died a violent death after total thyroidectomy, regardless of the care taken during the operation. Horsley, even though he was a clinician as well as an experimental physiologist, saw control over biological processes as the most reliable method for acquiring knowledge about the functions of the body. He had not observed myxoedematous symptoms in all his animals either, he admitted. But the fact that the symptoms, or some of them, were absent in some of the specimens was immaterial for the results as a whole, he held. This is an example of how experimental results did not necessarily foster consensus among investigators. The observations themselves did not indicate which of the various effects of the operations were relevant for answering the questions posed by the experimenter. Nor did they determine which observations had to be rated as valid and which were to be discarded as flukes.

⁵⁵⁰ Horsley, "Experimental and Clinical Contributions of Thyroid Tissue Replacement."

To Pflüger, Horsley's response was equal to a declaration of war. His charges now turned to insults. He questioned Horsley's visual faculty as well as his surgical abilities and insisted that myxoedematous symptoms never occurred after a professionally performed radical extirpation of the thyroid gland. A line of argument of this kind—i.e. explaining a postulated causal connection between two observed events (operation and symptom) with the influence of a third factor (errors on Horsley's part)—can never be refuted entirely, as every causal relationship can be questioned by referring to the effect of an additional third factor. One can see why observations alone do not prove causal relationships. In order to arrive at a conclusion in this regard, aspects unrelated to the experiment itself have to be taken into account, such as plausibility criteria that have been extrapolated from other kinds of experiences. Pflüger, for example, rather believed in "experimental errors a hundred times" before he accepted a result that seemed implausible to him.⁵⁵¹

A further exchange of blows hardened the opponents' fronts. Pflüger now initiated a major research project on monkeys. In these experiments, thyroid removal was followed by myxoedema. Then he tried something new: he removed only the parathyroid glands and left the neighbouring thyroid gland intact. This procedure led to severe tetany in the animals. The same thing happened when he severed the inferior thyroid artery of the thyroid axis' thyrocervical trunk, and thus the blood supply that is shared between the thyroid and the parathyroid glands, but left the organs themselves in place. Based on this observation, Pflüger constructed a new line of argument. First, he stated, since the removal of the thyroid gland caused myxoedema in the monkeys, this organ must somehow be involved in regulating the body's metabolism. In Pflüger's experiments, however, the transplantation of thyroidal tissue

⁵⁵¹ R. Rosemann, "Pflüger's Lebenswerk," *Pflüger's Archiv für die gesamte Physiologie des Menschen und der Thiere* 222 (1929): 562.

failed to reverse the pathologic effects of the thyroidectomies.⁵⁵² The thyroid therefore apparently relied on an additional factor to be effective, and this additional factor, Pflüger asserted, was the nerve supply of the organ. Secondly, the interruption of the blood supply between the parathyroid and thyroid glands also produced this effect, meaning that this connection was of major importance as well. Pflüger's understanding was that there existed nerve centres in the parathyroid glands that were responsible for regulating the internal secretion of the thyroid gland. These nerve centres, together with the internal secretion, were responsible for lowering the metabolic rate which was raised via a different neural route, namely from the central nervous system to the brain. Pflüger then designed a model of antagonistic neural metabolic regulation with the thyroid/parathyroids and the brain as the corresponding target organs. He corroborated his thesis with many analogous examples of regulatory processes in living organisms. Metabolic rate regulation was for him yet another instance of a universally valid functional principle.⁵⁵³

Pflüger's theory did not contradict Horsley's and Murray's organ-centred conception *de facto*, even though he kept insisting that his results refuted them both. In subsequent disputes, the German physiologist lost even more ground because many of the experimental results he had predicted were either too inconsistent or else had failed to materialise.

In the end, Pflüger acknowledged the connection between myxoedema and the internal secretion of the thyroid gland.⁵⁵⁴ In his last contribution to the subject—Pflüger died in 1910—he even defended himself against the accusation that he was a fundamental opponent of the theory of internal thyroid secretion who only accepted neuronal explanations for

⁵⁵² The difficulties associated with replicating this procedure have been discussed before at the end of section 5.2.

⁵⁵³ Eduard Pflüger, "Über die Natur der Kräfte durch welche die Schilddrüse den Stoffwechsel Beeinflußt," *Pflüger's Archiv für die gesammte Physiologie des Menschen und der Thiere* 119 (1907): 227–248.

⁵⁵⁴ Eduard Pflüger, "Parabiose und das Myxödem," *Pflüger's Archiv für die gesammte Physiologie des Menschen und der Thiere* 124 (1908): 633–638.

myxoedema.⁵⁵⁵ In light of the overall debates on the subject, Pflüger was evidently attempting to extricate himself from his ultimately hopelessly isolated position.

5.8. FOSTERING PROFESSIONAL INTEREST

Even strict adherence to the principles of controlling life processes in the physiological laboratory did not necessarily lead researchers and the practitioners of the clinic to the idea of organ replacement therapy, however. As we have seen in the case of the *Report on Myxoedema*, the experimental results obtained by Horsley left a certain scope for divergent interpretations—not just for the reader, but also for their fellow clinicians on the committee, most of whom came from internal medicine.

How researchers made use of this interpretive scope determined the direction taken by continuing research. For example, they could have regarded the counterarguments against the central role of the thyroid in myxoedema as significant and abandoned all research on organ replacement.⁵⁵⁶ Instead, the majority of researchers stuck to the goal of gaining control over physical processes through the control of the assumed necessary cause. It was a direction that was obviously too attractive to abandon for a number of reasons. To a technologically orientated style of medical care, reducing complex medical problems to one decisive factor of organ function looked like a recipe for success. Focusing on the failing organ allowed doctors to regard medical problems as the problems of individual patients that could be solved within the framework of professional clinical medical expertise. Social and political measures were then no longer needed; consulting a doctor was enough. The example of cretinism and myxoedema demonstrates how the organ replacement concept made it

⁵⁵⁵ Eduard Pflüger, "Experimental-Untersuchungen über das Myxödem," *Pflüger's Archiv für die gesamte Physiologie des Menschen und der Thiere* 128 (1909): 135.

⁵⁵⁶ As we have seen in Chapter 2, given Ord's own theory regarding the underlying disease mechanism of myxoedema, i.e. the accumulation of mucus in the dermis, this prospect would have been more viable than might be expected in retrospect.

possible for doctors to distance themselves from moral, political, and social questions, and thus avoid the professional frustration associated with an engagement in such domains.⁵⁵⁷

Differentiating more precisely within the medical profession, it becomes clear that the interests of doctors specialising in internal medicine and surgeons determined the direction of research on organ replacement therapy—and not, as may be expected, the physiologists of the laboratory. By focussing on one organ, controlling a circumscribed part of the body became decisive for controlling associated diseases. The specialists in local manipulations of the body were the surgeons, whilst the physicians broadened the former's approach to address the body as a system. Thus, these two groups in tandem were able to focus their attention on this necessary cause in the genesis of disease. They could now treat even more complex internal diseases successfully and thus extend their domain. In 1917, one author went so far as to characterise thyroid replacement therapy—and by extension organ replacement in general—as medicine's last possible area of expansion.⁵⁵⁸

Even contemporaries, such as John Gimlette, saw that the interest for the medical profession provided “a very decisive impetus for the organ replacement question.” Yet, only a small—yet very vocal—group of researchers worked on thyroid gland transplantation, for example, because “from the surgeon's standpoint [there was] no all too intense interest [in] creating possibilities for transplantation here.”⁵⁵⁹ Thus, the interests of surgeons and physicians alike in expanding their respective area of responsibility were an important factor in the development of the field of organ replacement therapy. This does of course not mean that either group was putting their own professional interests before the patient's welfare.

⁵⁵⁷ See: Schlich, “Changing Disease Identities,” 440–441.

⁵⁵⁸ Robert McCarrison, *The Thyroid Gland in Health and Disease* (New York: William Wood, 1917), 229.

⁵⁵⁹ Gimlette, *Myxoedema*, 137. For more general discussion on the history of tissue transplantation during the late 19th century, which included the grafting of thyroid tissue in the body of humans and animals alike, see: Moore, *Give and Take: The Development of Tissue Transplantation*.

Horsley, for example, was deeply concerned about the ethical implications of his practice.⁵⁶⁰ It may be assumed that doctors were engaging in the new style of therapy because they wanted to offer their patients a good form of therapy. But it is also clear that beliefs about what represents a good therapy should be assessed against the backdrop of competition between disciplines that was typical of the time. Surgeons like Horsley and Kocher fought all their professional lives for the recognition of their discipline in the face of what they saw as the dominance of internal medicine, whilst physicians struggled to at least try and maintain the *status quo* with the ascent of the laboratory sciences. Horsley's awareness of the disciplinary opposition between surgery, internal medicine, and the laboratory sciences can be seen in his reaction to the work on the committee on myxoedema, when he expressed his gratitude for the opportunity for interdisciplinary exchange, which he contrasted with the "common unwillingness to compromise" between the different factions of the medical profession.⁵⁶¹ In 1912, he complained about those colleagues of his, who "only recognise medical science as 'internal' medicine and regarded all else as nothing but technical specialty." When Theodor Kocher became the first surgeon to be awarded the Nobel Prize in 1909 it was also a triumph for Horsley's own discipline. Kocher used his Nobel address as an opportunity to give a detailed account of the recent rise of surgery in medical therapy. It was his conviction that surgery had moved beyond its traditional sphere of responsibility; after all, it was now providing treatment methods for the majority of the internal diseases, crowned by the most exciting cures.⁵⁶² Within half a century, surgery had made all organs of the body, including the heart and the brain, accessible to surgical interventions.⁵⁶³

However, in many instances, it becomes clear that organ replacement therapy stood in direct competition with internal medical treatments using the traditional array of medicaments at

⁵⁶⁰ See: Horsley, "Note on a Possible Means."

⁵⁶¹ Ibid., 288.

⁵⁶² Kocher, "Concerning Pathological Manifestations in Low-grade Thyroid Diseases," 330.

⁵⁶³ Ibid., 330–331.

medicine's disposal. Not only were those more readily available and cheaper, but to the average medical practitioner, let alone the vast majority of patients, the orthodox treatment methods appeared more trustworthy. Even Humphry Rolleston, one of the doyens of early endocrinology and a champion of advancing organotherapeutic treatment methods, noted as late as 1936 that the treatment of patients with a "pill containing nothing but the most common of pharmaceutical ingredients" posed "an especially dangerous rival" of organ replacement therapy and the main reason why treatments involving a meal of thyroid, subcutaneous injections of thyroid preparations, etc. had lost much of their original popularity.⁵⁶⁴ The two therapeutic modalities were closely related, however. The administration of tonics, etc. was often recommended to precede organ replacement therapy, and sometimes the sequence was reversed. Overall, progressive physicians and surgeons, however, tended to portray replacement therapy as the real, truly rational form of therapy, while pharmacotherapy represented the less rational, indirect kind of therapeutic approach. The main argument in favour of organ replacement therapy was the reconstruction, or at least very close approximation of the original physiological condition; "the original design" was to be imitated as closely and perfectly as possible.⁵⁶⁵ Only this rational type of physiological approximation would allow the body to use the organ's function in a way most closely to nature. Along these lines, Murray remarked that thyroid replacement therapy possessed "the great advantage over ordinary treatment measures in that it acts almost like a cure ... whilst the body's requirements set the standard."⁵⁶⁶ Organ replacement therapy eliminated the problems of having to subject the patient to a gruelling procedure of trial and error and, an even greater problem, that of poor patient compliance.⁵⁶⁷

⁵⁶⁴ Rolleston, *Endocrine Organs*, 304.

⁵⁶⁵ Schlich and Tröhler, *The Risks of Medical Innovation*, 221.

⁵⁶⁶ Murray, *Diseases of the Thyroid Gland: Myxoedema and Cretinism*, 181.

⁵⁶⁷ J. Lindholm and P. Laurberg, "Hypothyroidism and Thyroid Substitution: Historical Aspects," *Journal of Thyroid Research* 2011 (2011): 1–10.

Their claims to scientific authority sometimes caused both surgeons and physicians to end up competing with physiologists. Horsley emphasised, for instance, that surgery had made all organs accessible for direct observation. Surgical manipulation had made it possible to determine the conditions of an organ's function, which considerably increased the knowledge about the body's physiology. Physiologists had learned from surgeons to use anaesthesiology and asepsis in their animal experiments in order to prevent unnecessary pain and other disturbances in their experimental operations, thus making it possible to observe the physiological action of the organs without any artefacts or distractions.⁵⁶⁸ Clinical observations in fact supplied laboratory science with a continuous stream of research topics. They largely determined which phenomena the physiologists tried to elicit and to control in their laboratories.

5.9. CONCLUSION

It was in the context of the university style of medicine that organ replacement therapy was successfully established as a concept between the 1880s and the early 1900s. The setting of the modern research university enabled doctors and scientists to pursue a research ideal that called for the experimental control of life processes. It provided researchers with the time and material resources for developing the necessary procedures for reaching this goal. At the same time, the specific norms that governed knowledge production in this setting also created pressure to pursue only this particular goal. Thus, the conditions that characterise this particular setting enabled, and in a way enforced, the expensive and laborious laboratory research that led to the concept of organ replacement therapy. The motivation to develop new knowledge and new forms of therapy in this specific way was owed, to a great extent, to the characteristic situation of competing university disciplines. The different disciplines nevertheless used the same research methods, and their practitioners cooperated with each

⁵⁶⁸ John Benignus Lyons, "Sir Victor Horsley," *Medical History* 11 (1967): 361–373.

other in varying constellations. Above all, the laboratory sciences and clinical disciplines depended on a certain amount of collaboration with each other.

The innovation of organ replacement therapy thus took place neither in the laboratory alone nor exclusively in the clinic. It was at the interface of laboratory science and clinical medicine that the rise of the organ replacement concept occurred. This interface developed in late-nineteenth-century university medicine. Under these specific conditions, organ replacement rose as a procedure with which to control the biological processes of disease by controlling its decisive necessary cause. Thus, between 1880 and 1900 the idea that organ replacement therapy was an ideal treatment method, became firmly established.

– CHAPTER 6 –

CONSIDERING THE RISK: THE ETHICAL DIMENSION AND THE FAILURE OF ORGAN REPLACEMENT THERAPY IN CLINICAL PRACTICE

6.1. INTRODUCTION

In the preceding chapter, organ replacement therapy has been associated with questions and problems that went beyond the immediate scientific and medical domains. As a scientific and medical practice, it involved the values, norms, and cultural ideas of doctors, patients and society. How closely scientific problems were interrelated with problems outside their realm is demonstrated by the way that doctors and scientists implicitly or explicitly discussed ethical issues even in their professional publications. Some of these problems still connect to our modern times, such as in stem cell research or genomic medicine, which in itself can result in a form of replacement therapy. Related ethical questions were in a way already discussed between the 1890s and 1920s, though not usually in relation to the modern concept of “medical ethics.” These contemporary questions concerned above all the sources of the organs used for processing into organ replacement juices, the problem of testing the new therapeutic method on humans, and the varying degrees of information and consent of the patient. I will address, discuss, and contextualise these problems in the first part of this chapter.

The second part addresses the problem of determining the success of the new treatment. During the nineteenth century, the increasing scientification of medicine resulted in a vast arsenal of laboratory and test equipment, but also in expectations on the part of medical practitioners regarding the objectification of clinical findings and standardisation of medical

treatment. I will argue that both the ethical dimension and the determination of success with all its implications eventually led to a dissatisfaction of the medical profession with the new therapy.

6.2. USING ANIMAL ORGANS

A considerable amount of the thyroid tissue which was used for processing into extract for the treatment of thyroid insufficiency disorders came from animals. Sheep were the most common, as most other potentially suitable donor animals, such as monkeys, were notoriously hard to obtain. Over the course of his experiments on artificially induced myxoedema in animals between 1885 and 1887, Victor Horsley acquired his laboratory monkeys only with the help of the Royal Zoological Society and the London Zoo.⁵⁶⁹ But finding enough animals to serve as suitable organ donors for the increasingly high demands of organ replacement therapy both in terms of quality and quantity, was by far not the only issue doctors faced. Animal experiments were controversial to begin with, but their use as live organ donors for the treatment of human diseases kindled a new flame with some sections of society. The influence of the antivivisection movement should never be underestimated.⁵⁷⁰ In the end, finding itself under intense pressure from animal rights advocates, University College London saw it necessary to appoint a specialised caretaker to look after the animals used for Horsley's experiments on myxoedema.⁵⁷¹ However, the use of extracts gained from animal thyroids for the human organ replacement therapy provided another target for criticism. Even before the era of the widespread use of pharmaceutically prepared organ extracts, and later, synthetic hormone replacement medication, Brown-Séquard's organotherapy had outraged

⁵⁶⁹ Horsley, "Some Researches Carried Out During the Last Ten Years into the Functions of the Brain and the Thyroid Gland."

⁵⁷⁰ See Nicolaas Rupke's contributions to his edited volume on different aspects and national contexts of the antivivisection movement: Nicolaas A. Rupke, ed., *Vivisection in Historical Perspective* (London: Croom Helm, 1987).

⁵⁷¹ Horsley not only used monkeys, but kept pigs, dogs, cats, guinea pigs, and other animals over the course of his experimental trials.

the proponents of the English animal rights movement because the extracts were obtained from animals.⁵⁷²

On the other side of the animal controversy, an increasing number of medical scientists as well as general practitioners explicitly believed that the harvesting of thyroid glands and other organs from animals provided the ideal solution for most, if not all the problems experienced in terms of demand and supply. Especially among the more progressive medical scientists, animals were increasingly perceived as medically valuable commodities, as warehouses of constituents that could provide “*living* material in utterly perfect condition and unlimited quantity at any given time.”⁵⁷³ However, some may have feared an acceptance problem amongst their patients. In 1893, an anonymous letter to the editor of the *British Medical Journal* proclaimed that thyroid extracts from sheep—or any other animal for that matter—should not be procured because patients would not be willing to subject themselves to the procedure. The reason, they anticipated, was the patients’ “innate human prudishness.”⁵⁷⁴ Similarly, in a few cases patients were said to have refused having mild myxoedematous symptoms treated by the thyroid preparation because they believed “that ovine properties would be transferred [should they be] treated this way.”⁵⁷⁵ This view was subsequently stifled by the growing popularity of the treatment and its substantial therapeutic effects. Especially, as few doctors reported that their patients worried about losing or diminishing their identities as human beings if substances derived from animals were introduced into their bodies and metabolisms.⁵⁷⁶ However, whether the popularity of the treatment constituted a sense of acceptance on the part of the patients as much as of their physicians is open to discussion.

⁵⁷² Borell, “Origins of the Hormone Concept,” 63.

⁵⁷³ Harrower, *Outlines of Organotherapy*, 78. See also Shaw’s polemic text on the use of animals: H. Batty Shaw, *Organotherapy or Treatment by Means of Preparations of Various Organs* (Chicago: W.T. Keener, 1905).

⁵⁷⁴ *British Medical Journal*, “Thyroid Extract.”

⁵⁷⁵ Beadles, “The Treatment of Myxoedema and Cretinism, Being a Review of the Treatment of These Diseases with the Thyroid Gland, with a Table of 100 Published Cases,” 511.

⁵⁷⁶ On this theme in contemporary fiction, see: Hamilton, *The Monkey Gland Affair*, 67–69.

Warnings regarding the transference of animal qualities to the human recipient were mostly put forward by non-medical opponents to the thyroid treatment. These sceptics claimed, for instance, that, as the exact functions and properties of the thyroid remained largely unknown, this organ might continue to produce essential ovine qualities, which would then be carried by the circulation throughout the recipient's body, a view that took its legitimisation from the thyroid's characterisation as a blood-gland. The secretions of the organ of this primitive and 'amoral' animal would thus be able to potentially affect the mental and moral state of the recipient. The frequent application of thyroid replacement medicaments might, so a London based practitioner, theoretically lead to a mixture of both human and animal proteins and consequently result in a race that would effectively be a crossbreed between the ovine and human species. Because the recipients' entire body would be affected by this "bestialisation," one would be justified to suspect that women treated in this manner would give birth to sheep-like children, and same might happen on the father's side.⁵⁷⁷ More generally, eugenicists feared that this kind of hybridisation would gradually spoil and eventually poison the human species.⁵⁷⁸ At the same time, however, patients' revulsions might also have been directed against the members of their very own species, to the extent that patients felt more comfortable receiving thyroid extract from animals rather than from human thyroids. For that reason, despite the occasional availability of human thyroids, Murray and others would always opt for sheep thyroids because their patients, as Murray wrote, "were horrified at having tissue extract injected into their bodies from people they did not know, whereas sheep had something much more likeable about them."⁵⁷⁹

⁵⁷⁷ It is probably not too much of a conjecture to say that these reservations in the minds of the treatment's opponents conjured up images straight out of H.G. Wells' 1896 novel *The Island of Dr. Moreau* and might explain how novels of this kind evoked such strong feelings of horror and disgust among their readership; see Herbert George Wells, *The Island of Doctor Moreau* (London: Stone and Kimball, 1896).

⁵⁷⁸ Hamilton, *The Monkey Gland Affair*, 112–117.

⁵⁷⁹ Murray, *Diseases of the Thyroid Gland: Myxoedema and Cretinism*, 114.

6.3. THE PROBLEM OF GAINING HUMAN THYROID EXTRACT FROM THE LIVING OR DEAD

The problem of scarcity of suitable organs for processing emerged right at the beginning of organ replacement therapy. Researchers first began to use animal tissue because human tissue was exceedingly rare, outright unobtainable, or else unsuitable for therapeutic use.⁵⁸⁰ However, in cases where human thyroid could be obtained, a number of ethical and legal issues followed in its wake. The German physician and psychotherapist Albert Moll (1862--1939) summarised the outlines of this problem in his 1902 book *Ärztliche Ethik* in relation to a different case scenario. He explained, for example, how on the occasion of a necessary leg amputation he saw no reason for preventing the surgeon from removing some of the leg's skin for the purpose of grafting. The amputee would no longer consider "the leg his property and no one is hurt during the process."⁵⁸¹ Nonetheless, the removal of tissue or organs from a healthy individual, however, raised ethical problems. Even if the operation was "relatively insignificant" and therefore permissible, Moll thought that it should only be carried out after the "complete consent" of the donor had been obtained.⁵⁸²

Regarding the availability of human tissue for some of the first thyroid extracts, the most frequently used source were resected goitres. Since the ethical situation was essentially the same as with Moll's example of the amputated leg, the publications on the subject mention no reservations on the side of the medical profession. After all, the thyroid, after extirpation, was considered a waste product that was no longer the property of the patient who had

⁵⁸⁰ See amongst others: Beadles, "The Treatment of Myxoedema and Cretinism, Being a Review of the Treatment of These Diseases with the Thyroid Gland, with a Table of 100 Published Cases"; Shaw, *Organotherapy or Treatment by Means of Preparations of Various Organs*; Gimlette, *Myxoedema*; Murray, "The Life-History of the First Case of Myxoedema Treated by Thyroid Extract."

⁵⁸¹ Albert Moll, *Ärztliche Ethik: die Pflichten des Arztes in allen Beziehungen seiner Thätigkeit* (Stuttgart: Enke, 1902), 231.

⁵⁸² Ibid. Thomas Schlich uses this example to illustrate the historical significance of living organ donors. See: Thomas Schlich, *Die Erfindung der Organtransplantation: Erfolg und Scheitern des Chirurgischen Organersatzes* (Frankfurt: Campus, 1998), 256.

undergone surgery. Things, however, became much more problematic once doctors contemplated the use of tissue obtained from healthy thyroids. The English physician George Harrower, for example, let one of his myxoedematous patients wait until he found a potential donor who had to undergo some surgery on the neck region for something other than goitre, so that he could remove healthy thyroid tissue at the same time. In his report on the operation in 1904, Harrower emphasised that the donor had indeed given his consent to the procedure.⁵⁸³ One possible argument in favour of living human thyroid donations was the possibility of precise donor selection, which made it feasible—at least in theory—to obtain tissue from young and healthy blood relatives of the same sex.⁵⁸⁴ Thus, the English surgeon Jerome Logan described how healthy thyroid tissue was removed from the mother of a young woman suffering from myxoedema in order to prepare at least a preliminary course of thyroid juice for the treatment of her daughter.⁵⁸⁵ The main problem with this procedure was that thyroid gland removal, except in cases of severe goitre, was clearly of no use to the patient who had to undergo the procedure. Because of the possible damage to the donor as a result of thyroid deficiency, next to the dangers associated with the surgical intervention itself, surgeons and physicians alike had to proceed with extreme caution.⁵⁸⁶ Hence, removal, if practiced at all, had to be limited to very small sections and donors had to be prepared, apart from giving their consent, and had to be selected with extreme care.⁵⁸⁷ The majority of doctors evidently felt very uneasy about the procedure as a whole. “The notion that we might be harming human health is an extremely unpleasant feeling,” concluded the physician Christopher Larting in his short article.⁵⁸⁸ Although published reports about individual cases of

⁵⁸³ George Harrower, “Human Thyroid Juice Gained for the Treatment of Myxoedema in a Middle Aged Woman,” *Journal of Medical Science* 8 (1904): 14–15.

⁵⁸⁴ Murray, “The Treatment of Exophthalmic Goitre and Other Forms of Hyperthyroidism.”

⁵⁸⁵ Logan, “Surgical Thyroid Disease.”

⁵⁸⁶ Christopher Larting, “On Thyroid Surgery and Its Practical Importance,” *Archive of Clinical Science* 84 (1907): 212.

⁵⁸⁷ Logan, “Surgical Thyroid Disease.”

⁵⁸⁸ Larting, “On Thyroid Surgery and Its Practical Importance.”

partial thyroid removal sometimes emphasised the innocuousness of the operation, the donors' formal consent is rarely explicitly mentioned.⁵⁸⁹ The thyroid was usually removed due to goitre, or even internal diseases such as heart disease, or tuberculosis; yet, the use of thyroid tissue from diseased donors was heavily disputed because of the potential risks for the recipient. Doctors were warned much more about this latter aspect than the question of the donor's consent, or the question of ownership of bodily tissues.⁵⁹⁰ Thus, when an endocrinologist discussed the "problems one faces with the *in vivo* donation of thyroid tissue" in a survey in 1914, he dealt only with the possible harm to the recipient's health, not that of the donor.⁵⁹¹ An article in 1924 reminded doctors that failing to obtain the donor's consent could very well entail "legal questions."⁵⁹² Should the site of the operation become infected and diseased, and would thus subsequently have to be operated on as well, the patient or the patient's family could sue the surgeon or hospital involved in the procedure.

Finding voluntary living donors of healthy thyroid tissue was, however, equally difficult. Many specimens could not be used for living donations because their removal would seriously harm or even kill the donor. The risk of harming donors directed attention to the possibility of obtaining organs from the dead. Cadaverous tissue had already been used for the first human thyroid replacement therapy by Murray in a human in 1891, and it was thought that thyroid bodies could potentially come from stillborn babies, accident victims, or victims of violent crimes who had just died.⁵⁹³ Because of the obvious risk of harming a living donor, in 1901,

⁵⁸⁹ George Redmayne Murray, "Discussion on Exophthalmic Goitre," *British Medical Journal* 2 (1922).

⁵⁹⁰ Murray, "The Treatment of Exophthalmic Goitre and Other Forms of Hyperthyroidism"; Larting, "On Thyroid Surgery and Its Practical Importance"; Shaw, *Organotherapy or Treatment by Means of Preparations of Various Organs*.

⁵⁹¹ Anonymous, *A Manual of Biological Therapeutics* (London: Parke, Davis & Co., 1914).

⁵⁹² Cited after Woodruff, *The Transplantation of Tissues and Organs*, 502. For a brief historical overview see: Richard Burkewood Welbourne, *The History of Endocrine Surgery* (New York: Praeger, 1990), 124–128.

⁵⁹³ Anton Freiherr von Eiselsberg, *Die Krankheiten der Schilddrüse* (Stuttgart: Ferdinand Enke, 1901), 138, 186, 288. Murray had used human thyroid only once, and only with direct consent of the patient's family: Murray, "Notes on the Treatment of Myxoedema," 797; Murray, "The Life-History of the First

von Eiselsberg generally recommended the use of thyroid bodies from such recently dead donors.⁵⁹⁴ He did not, however, mention the presumed consent of either the dead or their surviving relatives. A special case was the thyroid removal in 1912 from a seventy-three-year-old woman who had just died of a “cerebral thrombosis.” A British surgeon reported that just before her death, her bed had been placed next to the physiological laboratory of his clinic, within walking distance to a patient suffering from severe myxoedema. The report states that neither of the patients had known anything about each other. Doctors prepared the donor’s throat for surgery while she was still alive. Right after her death they opened the throat “under completely aseptic conditions,” removed the healthy thyroid gland, put it into warm saline solution for short-term storage, and shortly afterwards began to prepare the organ for organotherapeutic treatment.⁵⁹⁵ Neither the consent of the dying patient nor the severe ethical problem of making preparations for the thyroid extirpation while she was still alive is mentioned anywhere in the article. However, the fact that the report was published in the *Lancet* shows that there were no particular objections to what, according to our standards today, would most certainly be an ethically questionable procedure.

In Scotland, the issue was even more problematic. Here, human thyroid tissue had only been considered as a potential therapeutic in 1914, when the surgeon Frank Lydston (1880–1958) considered the use of this organ from a human corpse to be practicable and promising. Nevertheless, the aversion to using the dead for science that prevailed in Scotland, as he wrote, made obtaining such organs difficult.⁵⁹⁶ Complicating matters even further was the

Case of Myxoedema Treated by Thyroid Extract,” 335; Murray, *Diseases of the Thyroid Gland: Myxoedema and Cretinism*, 49.

⁵⁹⁴ Eiselsberg, *Die Krankheiten der Schilddrüse*, 209.

⁵⁹⁵ Frank D’Abreu, “Preparation of Fresh Human Thyroid for the Treatment of Myxoedema,” *Lancet* 179 (1912): 1478–1479.

⁵⁹⁶ Frank G Lydston, “Implantations of the Thyroid Gland and Its Therapeutic Possibilities,” *Edinburgh Medical Journal* 100 (1914): 746. More recently, Caroline McCracken-Flesher discusses what she calls “a Scottish national trauma” about the use of human remains in medical research; see: Carolyn McCracken-Flesher, *The Doctor Dissected: a Cultural Autopsy of the Burke & Hare Murders* (Oxford: Oxford University Press, 2012).

fact that he needed thyroid glands from a certain category of donor: the dead had to be of a certain age, be victims of a violent death, be freshly deceased, and if possible, free from syphilis.⁵⁹⁷ Accordingly, he obtained thyroids from executed criminals. Lydston's conduct in these cases was severely attacked by the Scottish Anti-Vivisection Society. Animal rights advocates were often opposed to any form of exploitation of defenceless or dependent fellow creatures, and fought not only on behalf of animals but also for the protection of orphans, prisoners, and inmates of mental institutions alike.⁵⁹⁸ Lydston, who propagated *in vivo* donation in 1914, also advocated the popularisation of post-mortem organ donation. Why, he asked, should this "precious material be wasted" when in good hands and properly used, it could "contribute so much to the health, happiness, efficiency, and longevity of the human species"? This "biological" energy, he upheld, should be preserved and utilised.⁵⁹⁹

6.4. PATIENT CONSENT AND THE PROBLEM OF HUMAN EXPERIMENTATION

Organ replacement therapy was a new and ultimately experimental therapeutic measure. Using it on humans needed to be justified and, in published reports, doctors repeatedly weighed the risks and benefits against one another.⁶⁰⁰ As we know from Susan Lederer's work, contemporary antivivisectionists put such experimental interventions on humans in the context of animal experimentation and called them "human vivisections."⁶⁰¹ Occasionally even medical scientists made that connection and critically referred to total thyroidectomies

⁵⁹⁷ Lydston, "Implantations of the Thyroid Gland and Its Therapeutic Possibilities," 868–869.

⁵⁹⁸ Susan E Lederer, *Subjected to Science: Human Experimentation in America before the Second World War* (Baltimore: Johns Hopkins University Press, 1995), 112.

⁵⁹⁹ Lydston, "Implantations of the Thyroid Gland and Its Therapeutic Possibilities," 817.

⁶⁰⁰ The problem of harming the patient through treatment had already been raised in connection Kocher's goitre operations, involving radical thyroidectomies; see: Ulrich Tröhler, "Chirurgie und Ethik," *Gesnerus* 49 (1992): 119–135.

⁶⁰¹ Lederer discusses this subject thoroughly; see especially: Lederer, *Subjected to Science: Human Experimentation in America before the Second World War*, 27–50.

as *vivisection humaine*.⁶⁰² Similarly, some authors rejected the broad range of indications for thyroid replacement therapy, which they regarded as highly “questionable medical experiments.”⁶⁰³ They wanted to keep the risks as low as possible by implementing specific measures such as careful donor selection, which would avoid the transferal of disease along with the liquefied organ.⁶⁰⁴ Despite resistance, however, doctors emphasised the potential benefits of functional organ replacement therapy, and in doing so, often juxtaposed the targeted and very disease-specific effects of the therapy with the failure of previous, more conservative treatments, such as the use of stimulants, or even radical surgery. Another strategy for justifying the new procedures was to point out the patients’ desperate situation. Instead of letting people die, doctors felt they had the right to try functional replacement therapies as their last resort.⁶⁰⁵ On the other hand, some physicians claimed that they had assured themselves of the harmlessness, efficacy, and viability of the new treatment methods through a range of experiments.⁶⁰⁶ Time and time again, however, critics questioned the transferability of experimental results from animals to humans. Most often it was maintained that, compared to animal models, success in humans was much harder to achieve.⁶⁰⁷

Although reference to patient consent in relation to organ replacement therapy became increasingly common in the literature over the years,⁶⁰⁸ most medical-scientific articles did address the issue explicitly. For many experimentally inclined physicians and surgeons it was evidently sufficient to believe that they were acting with the patient’s welfare in mind, especially as patients themselves did not necessarily expect to be informed or to provide explicit consent in treatment situations. Holger Maehle has illustrated this mind-set with

⁶⁰² Ibid., 93.

⁶⁰³ Storer, “On Thyroid Replacement,” 44.

⁶⁰⁴ This problem is addressed very often; see, e.g.: Ibid., 43.

⁶⁰⁵ Ibid., 42.

⁶⁰⁶ James W. Christopherson, “The Efficacy of Treatment by Organ Extract,” *The Lancet* 2 (1912): 887–888.

⁶⁰⁷ Groves and Joll, “Thyroid and Its Treatment,” 1966; Kocher, “Über die Bedingungen erfolgreicher Schilddrüsenimplantation beim Menschen,” 548–549, 564.

⁶⁰⁸ Lydston, “Implantations of the Thyroid Gland and Its Therapeutic Possibilities.”

respect to Imperial Germany. Even though surgeons' traditional paternalism was challenged in court decisions that forced them to adopt the practice of seeking explicit patient consent, Maehle states that doctors maintained their paternalistic and maybe even patronising attitude:⁶⁰⁹ "While explicit refusal of a medical intervention would normally have been (reluctantly) accepted, patient consent was usually an implicit, tacit or 'silent' matter. The patient was expected to accept as a matter of course whatever treatment or measure the doctor, as the expert, felt necessary or appropriate."⁶¹⁰ And even though in Prussia patient information and explicit consent had been made compulsory for experimental procedures, in practice, the boundaries between experimentation and therapeutic intervention were often blurred.⁶¹¹

Sometimes, however, doctors were unable to ask the patient for their consent anyway. In 1893, the surgeon Henry Birkner described how a myxoedematous patient was unable to give her consent for thyroid replacement treatment due to her poor health: "With the hopeless condition, which would probably have soon led to her death, and no identifiable family available, the decision to proceed with the treatment was surely justified."⁶¹² Family commitments were often given as the grounds for myxoedema sufferers who were also mothers, as well as parents' wishes for children suffering from cretinism.⁶¹³ According to what Harrower described in 1904, it seems that many potential patients as well as their families were prepared to submit themselves to nearly anything that would help to improve their

⁶⁰⁹ Andreas-Holger Maehle, *Doctors, Honour and the Law: Medical Ethics in Imperial Germany* (Basingstoke: Palgrave Macmillan, 2009), 69.

⁶¹⁰ *Ibid.*, 78–79.

⁶¹¹ *Ibid.*, 83–84.

⁶¹² Henry Birkner, "Myxoedema and Cretinoid Degeneration," in *Clinical Papers*, vol. 357 (London: John Libbey, 1890), 33412.

⁶¹³ Horsley, "Some Researches Carried Out During the Last Ten Years into the Functions of the Brain and the Thyroid Gland"; D'Abreu, "Preparation of Fresh Human Thyroid for the Treatment of Myxoedema"; Harrower, "Human Thyroid Juice Gained for the Treatment of Myxoedema in a Middle Aged Woman"; Beadles, "The Treatment of Myxoedema and Cretinism, Being a Review of the Treatment of These Diseases with the Thyroid Gland, with a Table of 100 Published Cases."

condition.⁶¹⁴ Whether these patients believed that organ replacement therapy could improve their conditions, however, depended in turn on the information doctors provided them with. Especially in the context of children, as well as influential patients, some doctors were careful to obtain and document the patient's consent or that of their family. For instance, around the turn of the century, the Liverpool based physician Robert Morris had his patients sign a form that warned them about the risks and the entirely experimental nature of thyroid replacement therapy.⁶¹⁵ The Scottish physician Lydston, in his reports on organotherapeutic thyroid treatment, always mentioned the consent of the recipients or, in the case of severe mental impairment, that of their relatives.⁶¹⁶

Yet, one can also find evidence to the contrary. Above, we have discussed the case of Lydston's experimental treatment of prison inmates. Whether or not the recipients, who Lydston described as apathetic and weak, had wanted this form of treatment is not clear from the reports.⁶¹⁷ This kind of procedure was criticised by the Anti-Vivisection Society, which not only directed its criticism at the practice of obtaining organs from executed criminals but also thought that the self-determination of the recipients was jeopardised under prison conditions.⁶¹⁸ After Lydston had begun to use thyroid extract from animal sources for injection, however, an enormous demand for treatment arose amongst the prisoners. He did not hesitate to give in to their requests and was able to report on having performed some fifty such treatments.⁶¹⁹

⁶¹⁴ Harrower, "Human Thyroid Juice Gained for the Treatment of Myxoedema in a Middle Aged Woman."

⁶¹⁵ Lancet, "Liverpool," *The Lancet* 1 (1901): 1537.

⁶¹⁶ Lydston, "Implantations of the Thyroid Gland and Its Therapeutic Possibilities."

⁶¹⁷ Ibid.

⁶¹⁸ Lederer, *Subjected to Science: Human Experimentation in America before the Second World War*, 112.

⁶¹⁹ Frank G Lydston, "Further Therapeutic Possibilities of Organ Replacement," *New York Medical Journal* 105 (1919): 813–827.

In accordance with the paternalistic attitude of physicians in this period, the decision on whether to use animal or human thyroid extract was above all the doctor's, not the patient's.⁶²⁰ In some cases, even crucial information was intentionally withheld for reasons of experimental purity. Thus, in one case, doctors abstained from informing a patient in 1923 that she had received thyroid extract because they wanted to observe the effect without the interference of "psychological" factors.⁶²¹ In another example, dating from 1905, doctors for the same reason "painstakingly concealed" from a patient that the thyroid used for processing the emulsion had come from a homosexual prisoner for the same reasons.⁶²² Conversely, a homosexual prisoner had been treated with thyroid juice gained from a heterosexual without his knowledge.⁶²³

A similar problem arose when doctors wanted to observe the functional result of thyroid treatment by withholding additional therapy that could otherwise potentially obscure the results. Entirely unabashed, the London surgeon Leonard Williams wrote in 1909 that a child, suffering from myxoedematous symptoms and Bright's disease, had "of course" not been given any of its "usual medication" for the latter. After all, the whole point was "the complete and objective assessment of efficacy."⁶²⁴ Horsley, as well as Murray and Kocher, on the other hand insisted that they above all wanted to help the patient and that "the purity of the experiment *in vivo*" was of secondary importance.⁶²⁵

⁶²⁰ L. L. Stanley, "Thyroidal Substance Implantation," *Endocrinology* 5 (1921): 708–714; Stanley, "An Analysis of One Thousand Thyroidal Substance Implantations."

⁶²¹ Bainbridge, "Treatment with Human Thyroid Extract: Present Status and Future Possibilities."

⁶²² E. Kreuter, "Schilddrüsen und Therapie beim Menschen," *Zentralblatt für Chirurgie* 46 (1919): 539.

⁶²³ *Ibid.*, 540.

⁶²⁴ Leonard Williams, "Adenoids, Nocturnal Incontinence, and the Thyroid Gland," *The Lancet* 173 (1909): 1245.

⁶²⁵ George Redmayne Murray, "Three Cases of Sporadic Cretinism," *The Lancet* no. 2 (1909): 770–772; Kocher, "Über die Bedingungen erfolgreicher Schilddrüsenimplantation beim Menschen"; Horsley, "Some Researches Carried Out During the Last Ten Years into the Functions of the Brain and the Thyroid Gland." For the quote, see: Kocher, "Über die Bedingungen erfolgreicher Schilddrüsenimplantation beim Menschen," 512.

Occasionally, thyroid replacement therapy was even carried out on humans for purely experimental reasons without any therapeutic benefit in mind. Unsurprisingly, the criticism of the antivivisectionists on this point was directed particularly against this type of what they called “human vivisection.”⁶²⁶ Principally, the medical profession agreed that, especially for this kind of nontherapeutic medical intervention, “the consent of the test subject, given while fully of sound mind, was absolutely indispensable.”⁶²⁷ In 1902, Christiani performed such an experiment on a human patient: during the course of an unrelated operation, he implanted a reservoir of liquefied thyroid gland under the skin of a female patient who did not suffer from thyroid disease. In his article, he complained about the difficulty of finding volunteers who would give their consent for the procedure.⁶²⁸ In another example of human experimentation in the early 1920s, high concentrations of thyroid juice were given to volunteers with only partially functioning thyroid glands in order to examine the effect of the treatment in diminished thyroid activity. The express aim was to surgically examine the thyroid glands later on.⁶²⁹ These cases are particularly noteworthy, because the test subjects’ consent was explicitly mentioned in the publication.

Otherwise, the opportunity for follow-up examinations of partially affected thyroid glands after thyroid replacement therapy rarely came up. When a female patient, whose own partially active thyroid gland had been transplanted into her abdominal wall in 1911, underwent thyroid replacement therapy, and had to have an operation for another reason years later, the surgeons removed a small tissue sample of the organ. The patient’s consent is

⁶²⁶ Lederer, *Subjected to Science: Human Experimentation in America before the Second World War*, xv, 29–50.

⁶²⁷ Barbara Elkeles, “Die Schweigsame Welt von Arzt und Patient: Einwilligung und Aufklärung in der Arzt-Patienten-Beziehung des 19. und frühen 20. Jahrhunderts,” *Medizin, Gesellschaft und Geschichte* 8 (1989): 74.

⁶²⁸ Hector Christiani, “La greffe thyroïdienne chez l’homme,” *La Semaine Médicale* 24 (1904): 81–82.

⁶²⁹ For an unsigned literature review see: Münchner Medizinische Wochenschrift, “Bericht Zur Literatur” 72 (1925): 37.

not mentioned in the 1923 article.⁶³⁰ As a rule, however, doctors seemed to be hesitant to operate on a patient for the sole purpose of gaining a tissue sample, without a pertinent reason for the operation itself.⁶³¹

Often, however, doctors were not even able to obtain permission for post-mortem examinations of patients. Nevertheless, in 1910, despite the refusal of permission for an autopsy, two American surgeons evidently thought nothing of helping themselves to the thyroid gland of a patient who had suffered from myxoedema.⁶³² Another surgeon reported in 1923 that he had not succeeded “despite the greatest of efforts” in preserving the thyroid gland for histological examination after the death of the patient, because the body had been buried “due to a misunderstanding.”⁶³³

6.5. ETHICS AND ORGAN REPLACEMENT THERAPY FROM 1890 TO 1920

Many of the ethical problems discussed today in connection with organ replacement were already mentioned in the medical literature between 1890 and 1920. Certain subjects, however, did not turn up. Although many authors lamented the lack of suitable organs, the question of allocation—in other words, the distribution of this rare material—was not a subject they discussed. Only Lydston, in connection with his appeal for more willing organ donors, wrote in 1914 that only rich people and a small number of poor ones who were

⁶³⁰ J. H. Nattrass, “Autoplastic Thyroid Transplantation,” *British Medical Journal* no. 1 (1923): 1051–1052.

⁶³¹ Kocher, “Über die Bedingungen erfolgreicher Schilddrüsenimplantation beim Menschen,” 508. For a more general historical discussion of the issue, see: Cay-Rüdiger Prüll and Marianne Sinn, “Problems of Consent to Surgical Procedures and Autopsies in to Twentieth Century Germany,” in *Historical and Philosophical Perspectives on Biomedical Ethics: From Paternalism to Autonomy?*, ed. Andreas-Holger Maehle and Johanna Geyer-Kordesch (Aldershot: Ashgate, 2002), 73–94.

⁶³² F. C. Busch and T. Wright, “Three Cases of Myxoedema,” *Archives of Internal Medicine* 5 (1910): 32.

⁶³³ Emil Engel, “Zehn Jahre Beobachteter Fall einer Schilddrüsen Erkrankung,” *Deutsche Medizinische Wochenschrift* 50 (1923): 1378.

housed in mental institutions could profit from organ replacement therapy at the time.⁶³⁴ The question of the distribution of resources on the macroeconomic level—that is the question of costs—was not raised either. Because of their relatively small number, organ replacement therapies were not so important that their financial implications were discussed as a separate subject. Nevertheless, some authors did cite economic arguments in favour of this form of therapy. James Allan reported in 1903 a (ultimately unsuccessful) thyroid replacement therapy for a patient whose myxoedema had been rated so severe that she had not been allowed to stay in the hospital; yet, she could not afford the necessary medical care at home either.⁶³⁵ To Allan, this case merited thyroid replacement therapy, as the rapid and radical treatment was the only possibility of averting the patient's death.⁶³⁶

In summary, it is evident that ethical standards certainly existed during the early phase of organ replacement therapy. Doctors could and did by no means deal arbitrarily with patients. Nor did they usually ignore their patients' opinions on the proposed treatment. Also, they often found that they had to justify their procedures to their colleagues and the educated public.⁶³⁷ According to prevailing standards, the patient's welfare was the doctor's primary and frequently emphasised aim; any presumed deviation from it called for an explanation.⁶³⁸ As opposed to today, however, the patient's right of self-determination was usually subordinate to the doctor's "benevolent paternalism." In other words, it was primarily up to the doctor to decide what was best for the patient.⁶³⁹ In the field of organ replacement

⁶³⁴ Lydston, "Implantations of the Thyroid Gland and Its Therapeutic Possibilities," 917.

⁶³⁵ James W. Allan, "Treatment of the Thyroid Gland in Myxoedema," *British Medical Journal* no. 1 (1903): 523.

⁶³⁶ On this problem see also: Ulrich Tröhler, "'To Operate or Not to Operate?' Scientific and Extraneous Factors in Therapeutical Controversies Within the Swiss Society of Surgery 1913-1988," in *Essays in the History of Therapeutics*, ed. William F Bynum and Vivian Nutton (Amsterdam: Rodopi, 1991), 89–113.

⁶³⁷ On this subject, see: Elkeles, "Die Schweigsame Welt von Arzt und Patient: Einwilligung und Aufklärung in der Arzt-Patienten-Beziehung des 19. und frühen 20. Jahrhunderts," 83–84; Lederer, *Subjected to Science: Human Experimentation in America before the Second World War*, xv–xvi.

⁶³⁸ Elkeles, "Die Schweigsame Welt von Arzt und Patient: Einwilligung und Aufklärung in der Arzt-Patienten-Beziehung des 19. und frühen 20. Jahrhunderts," 83.

⁶³⁹ For a similar view, see: Elkeles (Ibid.)

therapy, opinions regarding the necessity of the patient's formal consent diverged, but over time, more and more physicians began documenting it. By the turn of the century, sensitivity on this issue had grown to such an extent that doctors increasingly had to take the legal consequences of their work into account. To what extent this kind of informed consent corresponded to today's standards, however, is another story.⁶⁴⁰ In general, awareness for the right of self-determination of both recipient and donor was less pronounced than today. The freedom of choice of the individual was not regarded as a core value of medical ethics until a later period in time. The ethics of organ replacement therapy were certainly no different from those of general medical ethics of the time, in that standards were relatively variable and much less explicit than later in the twentieth century.⁶⁴¹

6.6. THE PROBLEM OF ESTABLISHING THERAPEUTIC SUCCESS: MORPHOLOGICAL CONSIDERATIONS

The injection of liquefied organ extracts as a form of therapy was eventually abandoned in the wake of the development of the hormone concept. This was largely due to ethical issues relating to their administration, and because of the development of synthetic drugs that promised much the same effect. From today's perspective, the question arises how doctors even contemplated to harvest healthy thyroid tissue from a patient undergoing an unrelated operation. One may wonder whether physicians monitored the effectiveness of the substances—acquired at such a dear price— they injected into their patients, which leads to the more general question of how medical doctors were able to tell that their treatment was being effective or not. The criteria used for answering this question shifted in the course of the several decades during which physicians applied the treatment. Initially, they debated primarily whether organ replacement therapy could actually relieve or cure specific disorders

⁶⁴⁰ Ibid., 71.

⁶⁴¹ Ruth R Faden and Tom L Beauchamp, *A History and Theory of Informed Consent* (New York: Oxford University Press, 1986), 86–99.

at all. Subsequently, they mostly discussed whether it was really possible for liquefied tissues to have the same effect as the function of the original organ in the patient's body and, finally, whether the treatment could maintain this function in the long run.

At all times, the main question was whether the improvements observed in the patient's condition were owed specifically to the effects of the treatment and replaced function of the organ or not. If they indeed were, this would mean that doctors had gained access to one of the holy grails of medicine, i.e. being able to exert control over organ function, the necessary cause in specific diseases, and, consequently, exert control over those diseases. Many of the discussions in medical-scientific publications revolved around this aspiration. In the following, I will examine and evaluate some of the methods used to verify the success of the treatment and the arguments presented for and against the effectiveness of organ replacement therapy.

In essence, physicians had two kinds of criteria for the evaluation of the effectiveness of organ replacement therapy: morphological examination, i.e. the examination of the structure and form of the organ, and functional assessment, i.e. the evaluation of the effects of the treatment as based on the organ's supposed function. Palpation easily allowed the assessment of the affected organ, but was only practical if the tissue had not been removed, either through extirpation or the process of disease. Macroscopic assessment, however, was only of limited use, as it relied solely on the assumption that organ replacement therapy could actually have a curative effect on the affected organ. Murray reported in 1923 how, during the early years of the new therapeutic approach, he had received letters from all over the United Kingdom, asking him for a second opinion on the success of thyroid treatment by comparing the size of the organ before and after. However, Murray never openly advocated the curative power of organ replacement therapy, nor had he ever indicated any restorative effect on the original organ: "I could only marvel at the time wasted by those good doctors,

asking for advice on the inadvisable.”⁶⁴² But what struck him most was the vagueness of the descriptions provided. Apparently, most doctors were content with “an entirely subjective evaluation,” such as “thyroid apparently (!) enlarging or thyroid larger after administering thyroid juice, or smaller by [one fifth]” without providing an indication of the original size.⁶⁴³ To make matters more complex, macroscopic assessment, as others noted, did not even necessarily provide enough information on the presence of organ tissue in cases where organ replacement therapy was being administered in conjunction with partial transplantation.⁶⁴⁴

Macroscopic inspection was often complemented by a microscopic examination, especially in animal experiments. Histological follow-up examinations of macroscopically successful-looking restorative effects of organ replacement therapy almost invariably showed, however, that the original organ had not improved, or that the transplanted organ had not survived, but had simply been replaced by connective tissue.⁶⁴⁵ Over time, microscopic examinations gained in importance over the years. After 1900, histological changes were thoroughly examined and documented. Animal experiments on thyroid replacement therapy routinely included a histological follow-up examination of the organ.⁶⁴⁶ More importantly, perhaps, if their work lacked such examinations, authors were admonished to provide them.⁶⁴⁷ Such verification procedures eventually had practical consequences. Hence, the overwhelming

⁶⁴² Murray, “The Treatment of Exophthalmic Goitre and Other Forms of Hyperthyroidism,” 294.

⁶⁴³ Ibid.

⁶⁴⁴ Morley Currie, “Report of a Case of Myxoedema Treated with Benefit by a Partial Transplant and the Administration of Thyroid Juice,” *Canadian Medical Association Journal* 14 (1924): 627. Currie was not sure whether he was palpating thyroid tissue or only scar tissue.

⁶⁴⁵ E. von Leyden and Emil Pfeiffer, eds., *Verhandlungen des Kongresses für Innere Medizin, Dreiundzwanzigster Kongress. Gehalten zu München, vom 23.-26. April 1906* (Wiesbaden: Bergmann, 1906), 132; Georg Schöne, “Experimentelle Untersuchungen über den therapeutischen Effekt körperfremder Gewebe,” *Verhandlungen der Deutschen Gesellschaft für Chirurgie* 37 (1908): 174–178.

⁶⁴⁶ Alexis Carrel and Charles C. Guthrie, “Extirpation et replantation de la glande thyroïde avec reversion de la circulation,” *Comptes rendus hebdomadaires de seances et memoires de la société de biologie* 59 (1905): 412–413; Hector Christiani and E. Kummer, “Über funktionelle Hypertrophie überpflanzter Schilddrüsenstückchen beim Menschen,” *Münchener Medizinische Wochenschrift* 53, no. 2 (1906): 2377–2380.

⁶⁴⁷ E. Archibald Smith, “Thyroid Replacement,” *British Medical Journal* no. 1 (1911): 166. Some authors even apologised for the omission: Kocher, “Über die Bedingungen erfolgreicher Schilddrüsenimplantation beim Menschen,” 508.

number of negative findings in histological examinations by the end of the 1920s led most doctors to stop claiming that thyroid replacement therapy had any curative effect.⁶⁴⁸

Nevertheless, histological examinations did not in and of themselves provide unequivocal criteria for the assessment of therapeutic success. "Finding out whether pieces of tissue were alive or not [was] by no means always easy"; criteria included "visible signs of life, such as movement, contraction, ciliary action, [or] the ability to *proliferate*, to grow."⁶⁴⁹ However, this method did not preclude misinterpretations caused by confusing normal cell regeneration with the reparative effects of the treatment. Moreover, reparative changes had to be distinguished from degenerative ones.⁶⁵⁰ This task often proved difficult to accomplish. Signs which today would be interpreted as definitive proof of organ necrosis were sometimes regarded as indicators of success.⁶⁵¹

Moreover, the fact that these types of verification procedures were not always possible often caused uncertainty, and reports were often contradictory. Medical scientists began to have considerable doubts about the positive findings of researchers such as Murray, Horsley and Kocher.⁶⁵² It was especially difficult to clarify what the conditions were for assessing the success of treatments in humans. After all, as Schöne noted in 1912, one could not simply perform serial experiments on human patients.⁶⁵³ Particularly in the case of a success, that is, when treatment led to clinical improvement, it was ethically out of the question to perform the "*experimentum crucis*" by terminating treatment.⁶⁵⁴

⁶⁴⁸ Bainbridge, "Treatment with Human Thyroid Extract: Present Status and Future Possibilities."

⁶⁴⁹ F. Marchand, *Der Process der Wundheilung* (Stuttgart: Enke, 1901), 379. [Emphasis in original.]

⁶⁵⁰ P. P. T. Wu and Frank C. Mann, "Histologic Studies," *Archives of Surgery* 28 (1934): 908.

⁶⁵¹ F. C. Busch, T. M. Leonard, and T. Wright, "Further Results," *Journal of the American Medical Association* 51 (1908): 641.

⁶⁵² Woodruff, *The Transplantation of Tissues and Organs*, 506.

⁶⁵³ Georg Schöne, *Eigene Untersuchungen und Vergleichende Studien* (Berlin: Springer, 1912), 43.

⁶⁵⁴ *Ibid.*, 44.

It was far from unusual, however, for the affected organ's morphological condition not to correspond to its function. Medical researchers explained this phenomenon by claiming that the pathological changes in the patient's body changed the organ's function, so that it could no longer produce the same secretion. On the other hand, a tiny amount of thyroid tissue, liquefied and injected into the patient, could completely protect the organism from symptoms of deficiency.⁶⁵⁵ Because it would not do to "doubt clinical successes on the basis of unfavourable histological findings alone,"⁶⁵⁶ some authors explicitly distinguished the assessment of the clinical results from the—often times less favourable—histological findings.

6.7. FUNCTIONAL CONSIDERATIONS

While morphological considerations could potentially be useful for evaluating whether organ replacement therapy had a noticeable effect on the patient, physicians were not primarily interested in reconstructing morphology; they wanted to replace the lost function of an organ.⁶⁵⁷ That is why the experimental physiologists Alexis Carrel (1873–1944) and Hector Christiani, for example, clearly differentiated anatomical from clinical results in their researches.⁶⁵⁸ To them, organ function—or its replacement—was the decisive criterion of success. In order to assess function, however, doctors had to evaluate their patients' clinical condition with regard to specific disease entities. As demonstrated above, constructing specific functional insufficiency syndromes, such as myxoedema, on the basis of clinical observations had been a crucial step in establishing the organ replacement concept in the first

⁶⁵⁵ Murray, "The Life-History of the First Case of Myxoedema Treated by Thyroid Extract," 335.

⁶⁵⁶ George Redmayne Murray, "Indications for Surgical Treatment of Toxic Goitre," *British Medical Journal* 2 (1927): 774.

⁶⁵⁷ Horsley, "Some Researches Carried Out During the Last Ten Years into the Functions of the Brain and the Thyroid Gland"; Murray, "Three Cases of Sporadic Cretinism"; Murray, "The Life-History of the First Case of Myxoedema Treated by Thyroid Extract"; John Lynn-Thomas and Albert Kocher, "Gleanings from the Story of the Thyroid Gland: An Address Delivered to the South-West Wales Division of the British Medical Association," *British Medical Journal* 1 (1927): 91–94.

⁶⁵⁸ Carrel and Guthrie, "Extirpation et replantation de la glande thyroïde avec reversion de la circulation"; Christiani, "La greffe thyroïdienne chez l'homme."

place.⁶⁵⁹ For the thyroid, to which the concept was initially applied, the organ insufficiency syndrome myxoedema was then equated with spontaneously occurring clinical pictures. It was the disappearance of these specific symptoms after organ replacement therapy that made the concept convincing.

It is striking to observe how closely clinical and experimental physiological research related to each other in this context. Thus, many animal experiments served to reconstruct clinical pictures. Experimentally caused phenomena were compared with symptoms previously identified in humans, in our example after thyroidectomy.⁶⁶⁰ The disappearance of typical disease symptoms after thyroid replacement therapy, in combination with the re-appearance of these symptoms after the withdrawal of the treatment, however, was not only the key experiment for establishing the concept of organ replacement therapy but also the criterion for testing new organ replacement techniques. In 1908, for example, thyroid replacement therapy was said to have passed the “ordeal by fire” when the withdrawal of the treatment from a dog immediately caused fatal tetany and cachexia.⁶⁶¹

Assessing the successful organ replacement—and its proof—was only possible based on a suitable conceptualisation of the corresponding organ insufficiency diseases. Only after doctors had learnt to distinguish these organs morphologically and physiologically, i.e. functionally, were they able to come up with very specific deficiency symptoms for these organs, and only then were they able to determine whether treatment by organ replacement therapy was successful or not.⁶⁶² Constructing animal models, however, proved to be difficult,

⁶⁵⁹ This has been discussed in Chapter 4.

⁶⁶⁰ See: Wilson, “Internal Secretions in Disease: The Historical Relations of Clinical Medicine and Scientific Physiology,” 300. The examinations included taking measurements such as blood pressure, see, e.g., Busch, Leonard, and Wright, “Further Results,” 641.

⁶⁶¹ Garrè, contribution to the discussion, minutes published in *Verhandlungen der Deutschen Gesellschaft für Chirurgie*, “37th Congress,” 1908, 35.

⁶⁶² Shaw, *Organotherapy or Treatment by Means of Preparations of Various Organs*; Smith, “Thyroid Replacement”; Frank G Lydston, “Therapeutic Possibilities of Organ Replacement,” *New York Medical Journal* 100 (1914): 745–753, 812–819, 862–870, 913–918; Stefan Slater, “The Discovery of Thyroid

as we have discussed in relation to Horsley's thyroid experiments between 1884 and 1887. Therefore, in animal experiments—and even in human patients—death or survival were often the only definite indicators of the presence or absence of organ function.⁶⁶³ Proof of the effectiveness of thyroid replacement therapy, especially in cases where the striking myxoedematous symptoms were less pronounced, would frequently involve documentation of the patient's daily routine, ranging from details of bowel movements to mood swings.⁶⁶⁴ It is not surprising that objectification was hardly possible this way. The question of how thyroid replacement therapy affected the intelligence of cretinoid children, for example, tended to have an episodic character, too. A boy, for instance, "when asked what he wanted to be when he grew up, babbled: 'ojer' (soldier), and after the therapy had been started successfully, he firmly declared he wanted to be a 'professor.'"⁶⁶⁵

For the documentation of treatment-related changes, doctors often depended solely on patients' accounts. In order to determine the results of their thyroid replacement therapies, they send out questionnaires.⁶⁶⁶ Doctors also discussed the risk of distortion caused, for instance, by the fact that patients who were unhappy with their treatment were more likely to return the questionnaires than those who were satisfied.⁶⁶⁷ Generally, however, doctors placed more confidence in findings they could see for themselves than what patients reported. Hence one author wrote in 1906 that "*direct proof* for the function of the thyroid observed five weeks after commencing the [organ replacement] treatment is the lively colour

Replacement Therapy. Part 1: In the Beginning," *Journal of the Royal Society of Medicine* 104 (2011): 15–18; Welbourne, *The History of Endocrine Surgery*.

⁶⁶³ Explicitly stated in: Abelous, "La physiologie des glandules à sécrétion interne: Corps thyroïde et capsules surrénales," 278.

⁶⁶⁴ Murray, "The Life-History of the First Case of Myxoedema Treated by Thyroid Extract"; Allan, "Treatment of the Thyroid Gland in Myxoedema"; Gimlette, *Myxoedema*.

⁶⁶⁵ Murray, "Three Cases of Sporadic Cretinism," 771.

⁶⁶⁶ Kocher did so in 1914 and Murray in 1915. See: Kocher, "Über die Bedingungen erfolgreicher Schilddrüsenimplantation beim Menschen," 508; Murray, "The Life-History of the First Case of Myxoedema Treated by Thyroid Extract," 335.

⁶⁶⁷ Doyle, "Myxoedema," 104.

of the skin, the return of menstruation, the increased mental abilities.”⁶⁶⁸ However, the trustworthiness of scientists and doctors was another potential object of criticism. Schöne deplored that those observers who reported long-lasting successes with thyroid replacement therapy gained from ovine thyroids lacked the necessary scepticism for assessing “such an extraordinarily important ... experiment.”⁶⁶⁹ The problem of the scientific⁶⁷⁰ and moral⁶⁷¹ reliability of the authors of such reports was addressed repeatedly. Obviously, an observer’s trustworthiness was particularly dubious if his observation contradicted those of the majority of scientists.⁶⁷² For instance, as late as the 1920s, practitioners were still reporting regrown thyroid tissue while most of their colleagues had abandoned the idea.

In order to avoid such problems, doctors and scientists tried to standardize the criteria for successful therapeutic interventions. That is why practitioners attempted to infer the success of functional replacement from morphologically identifiable criteria. In case of thyroid replacement therapy, this was done by measuring the impact of the therapy on certain morphological parameters in the patient’s body. Body posture, muscular strength, skin condition, and hair regrowth provided suitable examples, for which doctors used complex testing methods that provided precise numerical values. Such measurements along such scales, for example, made it possible to assert that thyroid replacement therapy had improved a patient’s condition by 30 percent, for example.⁶⁷³ A further step towards objective clinical findings was photography. Murray, for example, liked to append his publications with

⁶⁶⁸ H. Cramer, “Theory and Therapy of Thyroiditis,” *The Lancet* 167 (1906): 1908. Emphasis added.

⁶⁶⁹ Schöne, *Eigene Untersuchungen und Vergleichende Studien*, 29.

⁶⁷⁰ Lydston, “Therapeutic Possibilities of Organ Replacement,” 815.

⁶⁷¹ Storer warned his colleagues to remain critical about scientific reports on the success of replacement therapy, “unless the reputation of the reporter is such as to give moral certainty.” Storer, “On Thyroid Replacement,” 41.

⁶⁷² See for example the report mentioned by Lydston which claimed an almost “complete regrowth” of the thyroid gland after commencing thyroid replacement therapy: Lydston, “Implantations of the Thyroid Gland and Its Therapeutic Possibilities,” 868.

⁶⁷³ Walter Langdon-Brown, *The Integration of the Endocrine System* (Cambridge: Cambridge University Press, 1935), 72.

photographs,⁶⁷⁴ although, as one critic commented, the camera was not necessarily deemed to be a suitable device for the scientific assessment of a patient's improvement.⁶⁷⁵

Another strategy to gain objective results consisted of measuring therapeutic effects with the help of laboratory methods. To obtain such measurements, doctors examined a sign directly linked to the action of the organ. For the thyroid, such a sign was the number of erythrocytes, or more specifically, the rise in red blood corpuscle counts.⁶⁷⁶ Evaluations of signs at this level, however, only became practicable after methods of measurement were introduced between 1915 and 1920 that required only a small amount of blood.⁶⁷⁷ The function of endocrine organs could at first only be truly represented through the indirect effects of hormones, even in the laboratory, and later it became possible to measure hormone concentrations in the blood itself.⁶⁷⁸

Nevertheless, even the most accurate measurements could not guarantee that it was really the effect of the treatment that was being measured. Stanley, for example, thought that by measuring glucose excreted in urine, he could prove that thyroid replacement therapy helped in cases of myxoedema—a claim that we now know was incorrect.⁶⁷⁹ In the end, concerning laboratory tests performed after starting a course of treatment with thyroid juice, researchers had to admit that hardly anything was actually known about the connection between the activity of the thyroid gland and the metabolic data they collected.⁶⁸⁰

⁶⁷⁴ Murray, "Three Cases of Sporadic Cretinism"; Murray, "The Life-History of the First Case of Myxoedema Treated by Thyroid Extract."

⁶⁷⁵ Hamilton Bailey, "Thyroid Treatment," *The Lancet* 1 (1927): 284.

⁶⁷⁶ Kreuter, "Schilddrüsen und Therapie beim Menschen," 539.

⁶⁷⁷ Robert Tattersall, "Quest for Normoglycaemia: a Historical Perspective," *Diabetic Medicine* 11 (1994): 618–635.

⁶⁷⁸ Ruben F. Gittes, "Endocrine Tissues," in *Transplantation*, ed. John S. Najarian and Robert L. Simmons (Munich: Schwarzenberg, 1972), 701; Borell, "Brown-Sequard's Organotherapy and Its Appearance in America at the End of the Nineteenth Century," 3–5.

⁶⁷⁹ Stanley, "An Analysis of One Thousand Thyroidal Substance Implantations," 787–794.

⁶⁸⁰ Walter Langdon-Brown, "The Birth of Modern Endocrinology," *Proceedings of the Royal Society of Medicine* 39 (1946).

6.8. THE PROBLEM OF CAUSAL ATTRIBUTION

A focal point for assessing the success of organ replacement therapy was the causal attribution of the observed effects. Even the best documentation could not determine which of the changes in the patient's condition had been caused by the therapy itself. After all, causal attributions are never self-evident. Crediting a particular treatment for the cure of a disease depends on the criteria applied.⁶⁸¹ These criteria tended to become more stringent over the course of the period investigated in this thesis. According to our current rules, therapeutic tests themselves must be controlled; that is, a group treated with a different therapy or a placebo must be included for comparison. The allocation to groups must be randomised. Furthermore, neither the test subjects nor the researchers are allowed to know who belongs to what group, i.e. the therapeutic test has to be double-blind.

In the period under investigation, clinicians and physiologists initially differed as to what appropriate standards to use in evaluating the effectiveness of organ replacement therapy. Physicians and surgeons primarily paid attention to their patient's symptoms. Whether clinical improvement could be attributed with any certainty to a specific cause was more often than not of secondary importance. Hence Murray defended organ replacement therapy in 1900 by asserting that only 12 per cent of the cases he treated had been 'failures'—that is, cases in which patients did not profit from the treatment.⁶⁸² However, this percentage does not explain whether the improvement of the remaining 88 per cent of the patients could be attributed to good long-term responses to the treatment. Physiologists, by contrast, had a very different approach. They aimed at controlling the test conditions so completely that they were able to draw unambiguous conclusions, at least according to their professional standards. This practice was, of course, much easier in animal experiments than under clinical

⁶⁸¹ Woolgar, *Science: The Very Idea*, 45–48.

⁶⁸² Murray, *Diseases of the Thyroid Gland: Myxoedema and Cretinism*, 127.

conditions. But the more stringent criteria used in physiological research increasingly came to dominate the clinical domain. As described above, the measurements in physiologists' laboratories were what turned the hypothesis of internal secretions into a 'scientific' subject, not Brown-Séquard's or Murray's clinical observations.

Basically, for an observation to be regarded as an effect of the thyroid replacement treatment, other possible causes of potentially unrelated phenomena had to be ruled out. Hence, as described above, one of the main points of dispute in scientific discussions on the concept of organ replacement therapy was whether a change in the patient's organism could be attributed *specifically* to the effects of the treatment or if it was an unspecified 'side-effect,' or even an entirely unrelated event of the procedure. In animal experiments, researchers sometimes created control groups of animals that were subjected to the same measures as during regular treatment, only without the thyroid juice itself.⁶⁸³

However, as with many diseases, doctors were just not able to rule out at least the possibility of spontaneous improvements in cases of myxoedema, independent of therapy. Thus, the causal attribution to thyroid replacement therapy remained debatable. A typical cause of such spontaneous improvements could be the action of a still active part thyroid gland in cases of only moderate myxoedema.⁶⁸⁴ Clear-cut evidence for the effectiveness of thyroid replacement therapy only existed when remaining activity of any original organ tissue could be ruled out with certainty. In animal experiments the receiving subject's own thyroid had to be removed carefully and completely; in humans it had to have lost its function completely. If, in humans, practical difficulties made complete removal impossible, as in all the cases of

⁶⁸³ Horsley, "Some Researches Carried Out During the Last Ten Years into the Functions of the Brain and the Thyroid Gland"; Ginn and Vilensky, "Experimental Confirmation by Sir Victor Horsley of the Relationship Between Thyroid Gland Dysfunction and Myxedema"; Horsley, "Thyroid."

⁶⁸⁴ Seemingly 'spontaneous' cures were especially relevant in the case of thyroid replacement therapy because experience had often shown that the clinical picture had improved seemingly independent, which could be explained by the existence of remaining active thyroid tissue; see Woodruff, *The Transplantation of Tissues and Organs*, 491.

myxoedema that did not and never would have to undergo total thyroidectomy, causal attribution remained ambiguous. Hence, a frequently mentioned requirement for these kinds of cases was a thorough morphological examination to identify all possible remainders of the patient's organ. In an animal experiment, the attribution could then happen by way of stopping the treatment, because the symptoms of thyroid insufficiency should then reappear. But, for obvious reasons the same could not be done easily with a human patient in whose case only a post-mortem autopsy would provide assurance. In one case of a supposedly curative course of thyroid replacement therapy in a child, for instance, the investigators found a small piece of the patient's own thyroid during the post-mortem examination, the existence of which retrospectively explained why the child had not shown any signs of hypothyroidism.⁶⁸⁵

Determining the cause of the disappearance of specific symptoms was naturally closely connected to what was thought to be the original cause of their appearance. Thus, doctors even disputed to what extent the multifarious symptoms of thyroid insufficiency had anything to do with the failure of the gland function in the first place.⁶⁸⁶ Even less clear was the causal connection between the wellbeing of the patient and the effects of the replacement treatment. A patient could feel well, claimed an anonymous author in the *British Medical Journal* in 1910, in spite of a failed treatment, or even specifically because the treatment had no effect at all in the first place.⁶⁸⁷

Often, a fair amount of suggestion seemed to be involved, for example, in the recovery of a patient's physical and mental equilibrium after commencing thyroid replacement therapy.⁶⁸⁸ Similarly, when doctors reported on the positive impact of the treatment in cases of

⁶⁸⁵ D'Abreu, "Preparation of Fresh Human Thyroid for the Treatment of Myxoedema."

⁶⁸⁶ Bainbridge, "Treatment with Human Thyroid Extract: Present Status and Future Possibilities," 497.

⁶⁸⁷ *British Medical Journal*, "Thyroid Questions" no. 2 (1910): 145.

⁶⁸⁸ Storer, "On Thyroid Replacement," 45.

cretinism, they had to be careful to distinguish the effect of the treatment itself from the unspecific influences on the patient, for “already the mere change in the environment, the influence of the nursing and medical personnel, the mere stimulus of the procedure could bring influences to bear that could lead to a more active participation in the surroundings, if only of a temporary nature.”⁶⁸⁹ Which kinds of effects could then actually be attributed to suggestion or environmental influences remained an open question. Hence, a researcher who performed thyroid replacement therapy in 1922 thought it was out of the question that psychological factors exercised an influence on symptoms such as the loss of hair, grey skin, or the loss of muscular strength.⁶⁹⁰ Another argument against the mere effect of suggestion was that researchers who performed animal experiments observed similar results.⁶⁹¹ A kind of placebo control can also be found in the literature: to those researchers who assumed that organ replacement therapy had no practical effects whatsoever, every instance of this therapy was a placebo intervention. If effects failed to appear, this observation was judged as correct and free of suggestion.⁶⁹² If, however, long-lasting cures were reported, “the belief in the miraculous effects” of this form of therapy had obviously worked.⁶⁹³

Another confounding factor was the continuation of other forms of therapy. Tonics, psychiatric care, or specialised diets were often continued during thyroid replacement therapy. In order to rule out the influence of conflicting methods of treatment, some researchers purposely stopped all other forms of therapy.⁶⁹⁴ By contrast, Theodor Kocher and George Murray expressly put the welfare of the patient before “the purity of the experiment

⁶⁸⁹ Bainbridge, “Treatment with Human Thyroid Extract: Present Status and Future Possibilities,” 495.

⁶⁹⁰ Stanley, “An Analysis of One Thousand Thyroidal Substance Implantations,” 792–793.

⁶⁹¹ Brandt and Liescheid, “Klinisches und Experimentelles zur Frage des Myxoedems,” *Zeitschrift für urologische Chirurgie* 12 (1923): 460–466.

⁶⁹² Lynn-Thomas and Kocher, “Gleanings from the Story of the Thyroid Gland: An Address Delivered to the South-West Wales Division of the British Medical Association,” 93.

⁶⁹³ *Ibid.*, 94.

⁶⁹⁴ Brandt and Liescheid, “Klinisches und Experimentelles zur Frage des Myxoedems,” 465.

in vivo.”⁶⁹⁵ Their patients often continued to receive a conservative therapy long into their thyroid replacement treatment. There were even cases when the therapy was declared a success when clinical improvement only began in combination with hypnosis therapy. Tetanic symptoms that persisted despite the therapy were declared to be of the functional type and were consequently treated successfully with hypnosis alone.⁶⁹⁶

The therapeutic studies and reports that were published between 1891 and 1920 thus do not correspond to today’s standards, either in documentation, their choice of data, or in their causal attributions.⁶⁹⁷ As a historian, I am therefore unable to make a valid statement about how well the organ replacement therapy worked. However, it is still relevant to ask the question how contemporaries thought about the therapy. The application of ever more stringent criteria explains the increasing disenchantment of the profession with the feasibility of thyroid replacement therapy. Yet, at the same time, the fact that these criteria were only gradually accepted explains why doctors continued to have hopes for organ replacement therapy for so long.

6.9. CONCLUSION

The development and establishment of the concept of organ replacement therapy had been completed by about 1900. Determining whether organ replacement therapy made sense in principle had by now become less and less a concern. Its validity had been established as a scientific fact, particularly in connection with the concept of internal secretions, and was no longer in need of proof. Organ replacement therapy was considered an ideal, albeit temporary, therapy. The only remaining stumbling stone was in its long-term practical

⁶⁹⁵ Kocher, “Über die Bedingungen erfolgreicher Schilddrüsenimplantation beim Menschen,” 510; Murray, “The Life-History of the First Case of Myxoedema Treated by Thyroid Extract,” 335.

⁶⁹⁶ Groves and Joll, “Thyroid and Its Treatment,” 1965–1967.

⁶⁹⁷ On the problem of experience with therapeutic methods and their objectification, see: Ulrich Tröhler, “Was ist Therapeutische Erfahrung? Die historische Entwicklung der Therapiebewertung zwischen subjektiv sicherem Wissen und objektiv wahrscheinlichen Kenntnissen,” *Deutsches Ärzteblatt* 88 (1991): B–2156–B–2162.

application, but even this problem did not affect the validity of the fundamental rationale, as Henry Birkner emphasised in 1890.⁶⁹⁸ Replacing a deficient organ was, as Murray wrote in 1909, the “obvious” thing do to.⁶⁹⁹

The general acceptance of the concept of thyroid replacement therapy also marked the beginning of endocrinology. While the early inventors of the organ replacement concept were also the pioneers of the future field of endocrinology, in the twentieth century the field followed its own separate trajectory. In the 1920s, endocrinology established itself as a new scientific endeavour: textbooks were published, a professional association was formed, and a specialised journal was established.⁷⁰⁰ This new field specified the explanation of organ function in a new way. The organs themselves became secondary; instead, scientists focussed on specific substances that they examined in terms of their coordinative function within the human body. Ernest Henry Starling coined the term ‘hormone’ for these substances.⁷⁰¹ Hormones were defined as messenger substances produced by the endocrine glands. Like nerves, they were able to control physiological processes. Thus, the endocrine system joined the nervous system as a coordinating mechanism of the body.⁷⁰² Researchers could isolate these hormones and examine them in the laboratory with established experimental physiological methods.⁷⁰³ Endocrinologists were therefore not that interested in organ replacement therapy anymore; their preferred method of treatment was hormone therapy—a pharmaceutical mode of therapy. To hormone researchers, experimental organ

⁶⁹⁸ Birkner, “Myxoedema and Cretinoid Degeneration,” 3408.

⁶⁹⁹ Murray, “Three Cases of Sporadic Cretinism,” 772.

⁷⁰⁰ Medvei, *History of Clinical Endocrinology*, 213–214.

⁷⁰¹ Starling introduced the term ‘hormone’, as well as the concept of hormones as chemical regulators for the body’s metabolism in the Croonian Lectures in 1905: Ernest H Starling, “Croonian Lecture: On the Chemical Correlation of the Functions of the Body I,” *The Lancet* 2 (1905): 339–341; Ernest H Starling, “Croonian Lecture: On the Chemical Correlation of the Functions of the Body II,” *The Lancet* 2 (1905): 423–425; Ernest H Starling, “Croonian Lecture: On the Chemical Correlation of the Functions of the Body III,” *The Lancet* 2 (1905): 501–503; Ernest H Starling, “Croonian Lecture: On the Chemical Correlation of the Functions of the Body IV,” *The Lancet* 2 (1905): 579–583.

⁷⁰² Borell, “Origins of the Hormone Concept,” 131–198.

⁷⁰³ Borell, “Setting the Standards for a New Science: Edward Schäfer and Endocrinology.”

replacement therapy by means of liquefied organs of humans and animals had been nothing but a preliminary stage followed, if possible, by the administration of hormones. For them, thyroid juice, or other organ extracts for that matter, was thus a stop-gap measure as long as scientists were unable to get hold of the hormone itself.

At the same time, clinical medicine and pathology broke away from their close connection to the nascent field of endocrinology. As shown in the preceding chapters, doctors had entirely concentrated on the replacement of organs with internal secretions, most prominently the thyroid gland. “Thyroid replacement and the many nice experiments done on it were actually the incentive for numerous other organ replacement approaches, some done by clinicians, some done by pathologists,” wrote Horsley in 1906.⁷⁰⁴ The results of thyroid replacement therapy had convinced doctors and scientists of the value of “*substitution therapy* (which tries to replace the malfunctioning organ for the organism),” and thus of organ replacement in general.⁷⁰⁵

By 1920, most animal experiments no longer aimed at elucidating the functions of particular organs but rather at determining the conditions of successful organ replacement therapy. The enormous interest in this kind of therapy peaked in the decade between 1891 and 1910. In 1906, Horsley noted that there was a “vast amount of literature” on organ replacement therapy, especially the thyroid gland.⁷⁰⁶ After the rather sceptical mood of 1890/91, a new optimism ruled the day from 1905 onwards. “Not only laymen but also the hearty types among doctors [found it] possible that the era was no longer distant when doctors would manage to replace a diseased organ’s function also in humans by using the essence form

⁷⁰⁴ Horsley, “Experimental and Clinical Contributions of Thyroid Tissue Replacement,” 151.

⁷⁰⁵ M. Jabouley, “La greffe de corps thyroïde et de capsules surrénales dans les maladies de ces glandes,” *La Médicale Revue Lyonnaise de Médecine* 84 (1897): 399–400.

⁷⁰⁶ Horsley, “Experimental and Clinical Contributions of Thyroid Tissue Replacement,” 154.

another person or perhaps even an animal,” wrote a researcher as late as 1913.⁷⁰⁷ However, this kind of enthusiasm was no longer standard by that time, as the mainstream medical opinion had already changed by then. Disagreement over causal attribution, severe ethical issues and the establishment of long-term success of the treatment, as discussed above in this chapter, all took its toll.

The majority of experts at that time thought that the limitations of thyroid replacement therapy applied equally to all organs. Consensus by the 1920s was that organ replacement therapy was an ideal, but unfortunately utopian, therapeutic method. In 1924, the surgeon Frederick Charles Pybus (1883–1975) of Newcastle-Upon-Tyne summed up the state of the art: organ replacement therapy may be the most rational treatment for many diseases, but until doctors had more knowledge about the fundamental phenomena involved, particularly the influence of chemical factors such as hormones, they would always fail long term.⁷⁰⁸ However, this is a different story, and one that must be told at a different time.

⁷⁰⁷ Rudolf Stich, “Über den heutigen Stand der Organtherapie,” *Deutsche Medizinische Wochenschrift* 39 (1913): 1865.

⁷⁰⁸ F. C. Pybus, “Notes,” *The Lancet* no. 2 (1924): 551.

FINAL CONCLUSION

This thesis has discussed the introduction and the use of organ replacement therapy in Britain. It has approached this subject, firstly, by examining the difficult and multifaceted history of thyroid insufficiency disorders, like endemic cretinism and goitre. Secondly, the introduction of myxoedema as a distinct clinical entity has been outlined; and finally, the professional debates surrounding the new therapeutic approach of organ replacement therapy as a cure for myxoedema have been analysed in their respective clinical application and scientific contexts. Although those are three very different themes, the chapters came together to explore those various motifs of medical practitioners and scientist by focussing on the thyroid gland and the associated disease entity of myxoedema as paradigmatic examples.

One of the main aspects of the introduction of organ replacement therapy into Britain and the medical community as a whole, which this thesis has demonstrated, is the one proposed by Thomas Schlich: invention rather than the realisation of a long-held dream. The first three chapter demonstrated the theoretical and practical difficulties experienced, first in the application of cretinism to the British context, and second in the re-conceptualisation of the underlying disease entity and its associated pathological mechanism. From its beginnings, the concept of organ replacement therapy was associated with a specific notion of disease causation. The example of the changing ideas from cretinism to myxoedema in Chapters 2 and 3 elucidates how this notion came about. The focus of this thesis has been on these diseases, because they were especially suitable for the development of organ replacement therapy which occurred in the context of a new understanding gained in those diseases in conjunction with a new understanding of the function of the thyroid gland. With cretinism, which had had fairly established clinical diagnostic methods, the difficulty lay in the older,

endemic characterisation of the disease, i.e. one that heavily relied on environmental factors, rather than its association with a specific, necessary cause. In most diseases characterised in such a manner, but especially endemic cretinism, the diagnosis was not infallible due to the possibility of false negative results. Although there appeared to be a burgeoning awareness of possible thyroid gland involvement in the first few papers published on the occurrence of cretinism in Britain during the 1850s and 1860s, this did not prove to be a revolutionary turning point, as the existing medical framework prevented the conceptualisation of the thyroid gland as an active pathological agent.

Chapters 2, 3, and 4 demonstrated the inventive aspect involved in the re-framing of cretinism into the new disease entity of myxoedema by focussing on the multifaceted involvement of clinical and laboratory scientists as well as general practitioners. Chapter 4 especially showed how the co-operation of several fields of expertise led to a re-evaluation of the previously professionally dismissed idea of organotherapy and how it was turned into the medically acceptable therapeutic approach of organ replacement therapy via liquefied thyroid glands as a cure for myxoedema. This re-evaluation relied on an expanded notion of the mid-nineteenth-century concept of internal secretions. This concept, in conjunction with a scientifically viable mode of result evaluation, led to the professional acceptance, not only of the organ replacement concept, but also of the causal association of the thyroid gland with myxoedema. The above examples show how the new understanding of thyroid deficiency diseases, the elucidation of their causal association with the thyroid gland, and the resulting therapeutic approach of organ replacement therapy was invented over the course of the roughly sixty years which this study encompasses.

The relationship between the clinic and the laboratory in the assessment and validation of the new disease entity and therapeutic approach was also explored in Chapters 2, 3, and 4, and the theme ran through Chapters 5 and 6. In Chapter 5 the changing status of the clinician was

examined in relation to the rise of university based scientific medicine with its focus on the creation of new knowledge through research, rather than of service functions such as patient care and student education. In this context, research practices were organised according to individual disciplines that often pursued the goal of knowledge production in competition. Funding, community support, and the mission to produce knowledge created conditions that permitted scientists and doctors at universities to pursue the epistemological ideal of controlling the processes of life and disease in the laboratory. This setting enabled the development of a modern type of scientific, therapeutically efficient medicine in the second half of the nineteenth century. However, not only the clinical aspect of medicine changed in this setting, but also the role of the scientifically oriented laboratory medical researcher. Above all, the laboratory sciences and clinical disciplines depended on a certain amount of collaboration. The innovation of organ replacement therapy thus took place neither in the laboratory alone nor exclusively in the clinic. It was at the interface of laboratory science and clinical medicine that the rise of the organ replacement concept occurred. Under these specific conditions, organ replacement resulted as a procedure with which to control the biological processes of disease by controlling myxoedema's necessary cause. In Chapter 6, we have seen how this new therapeutic approach created ethical questions regarding patient consent, the use of animal and human organs, and how to evaluate clinical success in patients. Especially the latter developments led to a more muted response to organ replacement therapy, which eventually resulted in it being judged a clinical failure. Although interest in the principles of organ replacement therapy remained, the approach was increasingly questioned on grounds of success evaluation, long-term viability, and ultimately the inability to determine the causal relationship between the onset of myxoedematous symptoms and the failure of the thyroid gland. Therefore, in Chapters 3, 4, and 6, we have seen how the underlying disease mechanism was invented, challenged, re-defined, with the

resulting therapeutic approach eventually being dismissed because of ambiguous data gathered both in the clinical and laboratory settings.

Continuing from the theme of the invention of organ replacement therapy in conjunction with developing knowledge about the thyroid gland and its associated disease entities, another aim of this thesis was to understand how this new knowledge was incorporated into the existing medical frameworks. Therefore, next to invention, change was also examined. Chapters 2 through 4 demonstrated that despite the status of knowledge about cretinism, myxoedema, and the thyroid gland having been different between 1883 and 1891, the groups of medical practitioners, be they clinicians or laboratory scientists, were able to grasp and change the competing disease concept and attempted to internalise it into their respective professional realm. This was especially the case with Victor Horsley who worked both as a clinical neurosurgeon and as an experimental physiologist. However, also researchers working exclusively in the laboratory, such as those experimenters who undertook some of the experiments proposed by Horsley, as well as pure clinicians, such as George Murray, mutually influenced one another in an attempt to both understand the physiology of the thyroid gland as well as its pathological and clinical relevance. This demonstrates that the different groups were capable of entering a mutually beneficial relationship while inventing and changing existing medical knowledge. Although the older notion of cretinism and the emerging concept of myxoedema had displayed somewhat different clinical pictures, and accordingly required different management strategies, the emerging concept of an underperforming thyroid gland transcended all this, and was adopted and utilised by clinicians and medical scientists. In Chapter 6, we have also seen that patients were aware of some of the issues surrounding the use of organ replacement therapy. These issues revolved largely around the use of animal organs, or those of prisoners, as raw material for the preparation of thyroid juice. This may have been due to the high profile nature of the discussion within the medical community whose practitioners seemed eager to contribute to the growing literature and consequently

made use of the therapy in their practice. Especially in the hospital, the use of organ replacement therapy has been shown to be taken up fairly rapidly. This may have been influenced by the close proximity of clinicians and laboratory scientists, beneficial for exchange of experiences and knowledge.

In addition to exploring these themes, this thesis has also contributed to and challenged the existing literature on some topics and has proposed new research in other areas. Overall, this thesis wants to show that it is worthwhile to refocus on seemingly old and established themes in the history of medicine, rather than constantly seeking out new historiographical areas of research.⁷⁰⁹ The first four chapters of this thesis, for example, have shown that it is well worth revisiting supposedly common historical ground and researching new primary and secondary material as a different side to a story can be constructed. Thus, while the early history of myxoedema has often been portrayed as an outright failure, as discussed in Chapter 3, this thesis has shown that although the results gathered during this early stage were indeed inconclusive, the results were nonetheless open-ended and flexible enough to establish a viable scientific and clinical framework that proved to be invaluable for the later construction of organ replacement therapy.

Furthermore, and somewhat in contrast to the existing literature on tensions between the clinic, especially elite physicians, and the laboratory,⁷¹⁰ Chapters 5 and 6 have shown that

⁷⁰⁹ This statement first appeared in Nancy Tomes and John Harley Warner, "Introduction to Special Issue on Rethinking the Reception of the Germ Theory of Disease: Comparative Perspectives," *Journal of the History of Medicine and Allied Sciences* 52 (1997): 16. However, in 2010 Thomas Schlich made the same statement with regards to the history of organ transplantation, see: Schlich, *The Origins of Organ Transplantation: Surgery and Laboratory Science, 1880-1930*, 8.

⁷¹⁰ Steve Sturdy, "Knowing Cases: Biomedicine in Edinburgh, 1887-1920," *Social Studies of Science* 37 (2007): 659-689; Steve Sturdy, "Looking for Trouble: Medical Science and Clinical Practice in the Historiography of Modern Medicine," *Social History of Medicine* 24 (2011): 739-757; Steve Sturdy, "Scientific Method for Medical Practitioners: The Case Method of Teaching Pathology in Early Twentieth-Century Edinburgh," *Bulletin of the History of Medicine* 81 (2007): 760-792; Christopher Lawrence, *Rockefeller Money, the Laboratory and Medicine in Edinburgh 1919-1930: New Science in an Old Country*, Rochester Studies in Medical History (Rochester, NY: University of Rochester Press, 2005); Lawrence, "A Tale of Two Sciences: Bedside and Bench in Twentieth Century Britain."

clinicians have frequently translated clinical problems into a form that experimental physiology could deal with, and *vice versa*. Exemplary figures in this respect have been Victor Horsley in London, George Murray in Newcastle-upon-Tyne, and Theodor Kocher in Berne. This is not to suggest that tensions did not exist; the main points of friction were perceived in areas such as patient care and experimental purity, causal attribution, and between thyroid replacement therapy and confounding factors such as additional modes of treatment. In addition, results achieved in the laboratory using animal models were not always translatable into clinical application, as Horsley's transplant experiments of the early 1890s have shown.

In examining attitudes towards ethical concerns, a further area of research could be proposed. Ideas about patient information and consent about new treatment methods, such as thyroid replacement therapy, and concerns regarding experimental purity demonstrate the changing attitude of responsibility towards patients at the interface of clinical practice and experimental research that have been introduced in Chapter 5 and expanded in Chapter 6. As we have seen, the Scottish physician Frank Lydston had advocated the use of organs from executed criminals as a source of human thyroids in the treatment of myxoedema. This attitude was severely criticised by the Anti-Vivisection Society, which sought to uphold the principle of self-determination of treatment recipients even under prison conditions. Further historical investigations could pursue the question whether Lydston's clinical experiments were a one-off event or whether the growing popularity of organ replacement therapy actually created a milieu in which such ethically questionable approaches became more common. Were they part of a richer history of human experimentation than the one that Susan Lederer has suggested in 1995? And how does it differ from the American context discussed in her work?

In addition to exploring these themes in relation to clinical practitioners and medical scientists, other actors have also played a recurring role in this thesis. The effect of ideas

created in the environment of a specialist community, the Committee for the Investigation of Myxoedema, of the Clinical Society of London, appeared in Chapters 2 and 3. The discussion of this group, which consisted of surgeons, physicians, and an experimental physiologist, suggests some of the reasons as to how these two supposedly competing groups of clinicians and scientists were able to enter into a productive relationship. In turn, individual voices from within the medical community have appeared in Chapter 4, as the actions of the two rather abstract groups being exemplified by the Committee cannot be explained without examining how individual doctors reacted to the results proposed. Patient concerns about the new treatment method have appeared briefly in Chapter 6. And the relationship between clinical practitioners and medical scientists was more broadly discussed in Chapter 5, where the mutually influential relationship between these two groups relating to ideas about the thyroid gland, myxoedema, and its treatment have been examined.

The origins of the ensemble of new concepts and practices that constitute myxoedema and the associated organ replacement therapy can thus be situated within a precise timeframe and context. They did not simply follow from the way medicine was practiced; nor were they the culmination of medical progress. Instead, the practice of organ replacement therapy, as well as the new disease entity of myxoedema depended on the existence of a view of the human body that assumed the possibility and desirability of replacing an organ's function. This view was part of the concept of organ replacement which emerged in the specific context of the experimentally oriented style of university medicine that was predominant in the late nineteenth and early twentieth centuries. Its emergence depended in turn on contemporary clinical and scientific practices as well as on the institutional and epistemological context in which these practices were embedded. Various social, scientific, and technical conditions thus needed to concur, as described in the chapters of this thesis, before organ replacement therapy could become part of the kind of medical reality that we are now familiar with.

BIBLIOGRAPHY

PRIMARY SOURCES (PRINTED, RE-PRINTED AND ARCHIVAL)

- Abelous, J. E. "La physiologie des glandules à sécrétion interne: Corps thyroïde et capsules surrénales." *Revue Générale des Sciences Pures et Appliquées* 4 (1893): 273–278.
- Adams, Joseph. "On Goitre and Cretinism." *The Medical and Physical Journal* 33, no. 6 (1815): 433–447.
- Allan, James W. "Transplantation of the Thyroid Gland." *British Medical Journal* 1 (1903): 268–269.
- . "Transplantation of the Thyroid Gland in Myxoedema." *British Medical Journal* 1 (1903): 711.
- . "Transplantation of the Thyroid Gland in Myxoedema, and of the Suprarenal Gland in Addison's Disease." *British Medical Journal* 1 (1903): 764.
- . "Treatment of the Thyroid Gland in Myxoedema." *British Medical Journal* no. 1 (1903): 523.
- Allen, Frederick M. *Studies Concerning Myxoedema*. Cambridge, Mass.: Harvard University Press, 1913.
- Ambrose, A. "Letter to the Editor in 'Letters, Notes, and Answers to Correspondents'." *British Medical Journal* 2 (1892): 163.
- Anonymous. *A Manual of Biological Therapeutics*. London: Parke, Davis & Co., 1914.
- Bailey, Hamilton. "Thyroid Treatment." *The Lancet* 1 (1927): 284.
- Bainbridge, William S. "Treatment with Human Thyroid Extract: Present Status and Future Possibilities." *American Journal of Obstetrics and Gynaecology* 5 (1923): 493–498.
- Ballet, G. "Cachexie Pachydermique (Myxoédeme, des auteurs anglais)." *Progrès Médicale* 8 (1880): 605–606.
- Barclay, Andrew Whyte. *A Manual of Medical Diagnosis: Being an Analysis of the Signs and Symptoms of Disease*. Philadelphia: Blanchard & Lea, 1862.
- Bardeleben, V. "Diskussionsbeitrag zu Kocher's 'Über die Kropfexstirpation und ihre Folgen'." *Verhandlungen der Deutschen Gesellschaft fuer Chirurgie* 12, no. 2 (1883): 4–9.
- Beadles, Cecil F. "The Treatment of Myxoedema and Cretinism, Being a Review of the Treatment of These Diseases with the Thyroid Gland, with a Table of 100 Published Cases." *Journal of Mental Science* 39 (1898): 343–355; 509–536.

- Bernard, Claude. *An Introduction to the Study of Experimental Medicine*. New York: Dover, 1957.
- . *Leçons sur les propriétés physiologiques et les altérations pathologiques des liquides de l'organisme*. Vol. 2. Paris: J.B. Baillière, 1855.
- Bettencourt, A. M., and J. A. Serrano. "Un Cas de Myxoedème Traité par la greffe hypodermique du corps thyroid d'un mouton." *La Semaine Médicale* 10 (1890): 294.
- Biedl, Artur. *The Internal Secretory Organs: Their Physiology and Pathology*. New York: William Wood, 1913.
- Birkner, Henry. *Endemic Goitre*. London: Churchill, 1883.
- . "Myxoedema and Cretinoid Degeneration." In *Clinical Papers*, 357:3393–3424. London: John Libbey, 1890.
- Blackie, George Stodart. *Cretins and Cretinism: A Prize Thesis of the University of Edinburgh*. Edinburgh: Maclachlan & Stewart, 1855.
- Brachet, Léon. *Observations de cachexie pachydermique de Charcot, myxoedème crétinoïde de sir William Gull et de Ord, par le Dr Brachet. Lecture faite au congrès des Sociétés savantes, à Aix-les-Bains, le 25 septembre 1882*. Paris: Gêrente, 1883.
- Brandt, and Liescheid. "Klinisches und Experimentelles zur Frage des Myxoedems." *Zeitschrift für urologische Chirurgie* 12 (1923): 460–466.
- British Medical Journal. "Animal Extracts as Therapeutic Agents." *British Medical Journal* 1 (1893): 1279.
- . "Dr. Brown-Séquard's Experiments: A Member of the Medical Profession Writes." *British Medical Journal* 2 (1889): 347.
- . "Dr. Brown-Séquard's Hypodermic Fluid." *British Medical Journal* no. 2 (1889): 29.
- . "Myxoedema and Cretinism." *British Medical Journal* 2 (1884): 1028–1029.
- . "Note on the Transplantability of the Thyroid Gland." *British Medical Journal* 1 (1888): 1490.
- . "Physiology in 1892." *British Medical Journal* 2 (1892): 1442.
- . "R. Brudenell Carter, R.R.C.S." *British Medical Journal* 2 (1918): 502–503.
- . "Report of the Clinical Evening of the Harveian Society." *British Medical Journal* 1 (1892): 22.
- . "The New Elixir of Youth." *British Medical Journal* no. 2 (1889): 446.
- . "The Pentacle of Rejuvenescence." *British Medical Journal* no. 1 (1889): 1416.
- . "The Recent Experiments of Dr. Brown-Séquard." *British Medical Journal* 2 (1889): 229.

———. “The Treatment of Myxoedema.” *British Medical Journal* 2 (1892): 965.

———. “Thyroid Extract in Myxoedema.” *British Medical Journal* 1 (1893): 252.

———. “Thyroid Grafting” 2 (1887): 590.

———. “Thyroid Grafting in Britain.” *British Medical Journal* 1 (1891): 216.

———. “Thyroid Questions” no. 2 (1910): 145.

Brown-Séquard, Charles-Éduard. “Des effets produits chez l’homme par des injections sous-cutanées d’un liquid retire des testicules de cobaye et de chien.” *Comptes rendus de Société de Biologie* 1 (1889): 415–419.

———. *Lectures of the Diagnosis and Treatment of Functional Nervous Affections*. Philadelphia: J.B. Lippincott, 1868.

———. “Note on the Effects Produced on Man by Subcutaneous Injections of a Liquid Obtained from the Testicles of Animals.” *The Lancet* 2 (1889): 105–107.

———. “On a New Therapeutic Method Consisting in the Use of Organic Liquids Extracted from Glands and Other Organs.” *British Medical Journal* 1 (1893): 1145–1147, 1212–1214.

———. “Seconde note sur les effets produits chez l’homme par des injections sous-cutanées d’un liquid retire des testicules frais de cobaye et de chien.” *Comptes rendus de Société de Biologie* 1 (1889): 420–422.

———. “Troisième note sur les effets des injections sous-cutanées de liquid testiculaire.” *Comptes rendus de Société de Biologie* 1 (1889): 430–431.

Brown-Séquard, Charles-Éduard, and Arsenne d’Arsonval. “De l’injection des extraits liquides provenant des glandes et des tissus de l’organisme comme method thérapeutique.” *Comptes rendus de la Société de Biologie* 9 (1891): 248–250.

Busch, F. C., T. M. Leonard, and T. Wright. “Further Results.” *Journal of the American Medical Association* 51 (1908): 640–642.

Busch, F. C., and T. Wright. “Three Cases of Myxoedema.” *Archives of Internal Medicine* 5 (1910): 30–36.

Campbell, G. Gordon. “A Case of Sporadic Cretinism.” *Montreal Medical Journal* (1899): 1899.

Carrel, Alexis, and Charles C. Guthrie. “Extirpation et replantation de la glande thyroïde avec reversion de la circulation.” *Comptes rendus hebdomadaires de seances et memoires de la société de biologie* 59 (1905): 412–413.

Charcot, Jean-Martin. “Myxoedème, cachexie pachydermique ou état cretinôide.” *La Gazette de l’hôpital* 1 (1880): 73–75.

Christiani, Hector. “La greffe thyroïdienne chez l’homme.” *La Semaine Medicale* 24 (1904): 81–83.

- Christiani, Hector, and E. Kummer. "Über funktionelle Hypertrophie überpflanzter Schilddrüsenstückchen beim Menschen." *Münchener Medizinische Wochenschrift* 53, no. 2 (1906): 2377–2380.
- Christopherson, James W. "The Efficacy of Treatment by Organ Extract." *The Lancet* 2 (1912): 887–888.
- Christopherson, Reginald. "Physiology of Glands." *The Lancet* 1 (1878): 1014–1017.
- Clinical Society of London. "Meeting, April 1884." *Transactions of the Clinical Society of London* 17 (1884): 36–49.
- . "Minute Book of the Clinical Society of London," 1888–1877. ClinSoc 16678.13 T23. Royal Society of Medicine.
- . "Report of the Council of the Clinical Society." *Transactions of the Clinical Society of London* 20 (1887): lx.
- . *Transactions of the Clinical Society of London*. Vol. 16. London: Longmans, Green, & Co, 1883.
- Clunn, T. R. H. "Myxoedema Following Haemorrhage." *British Medical Journal* 1 (1883): 312.
- Cobb, Ivo Geikie. *The Organs of Internal Secretion, Their Diseases and Therapeutic Application: A Book for General Practitioners*. London: Baillière, Tindall and Cox, 1921.
- Cramer, H. "Theory and Therapy of Thyroiditis." *The Lancet* 167 (1906): 1906–1909.
- Curling, Thomas Blizard. "Two Cases of Absence of the Thyroid Body, and Symmetrical Swellings of Fat Tissue at the Sides of the Neck, Connected with Defective Cerebral Development." *Medico-chirurgical Transactions* 33 (1850): 303–306.
- Currie, Morley. "Report of a Case of Myxoedema Treated with Benefit by a Partial Transplant and the Administration of Thyroid Juice." *Canadian Medical Association Journal* 14 (1924): 626–628.
- D'Abreu, Frank. "Preparation of Fresh Human Thyroid for the Treatment of Myxoedema." *Lancet* 179 (1912): 1478–1479.
- Doyle, L. "Myxoedema: Some Early Reports and Contributions by British Authors, 1873–1898." *Journal of the Royal Society of Medicine* 84 (1991): 103–106.
- Drewitt, F. G. D., Felix Semon, and William Miller Ord. "A Typical Case of Myxoedema." *British Medical Journal* 2 (1883): 1072–1074.
- Drobnick, Thomas. "Experimentelle Untersuchungen über die Folgen der Exstirpation der Schilddrüse." *Archiv für Experimentelle Pathologie und Pharmakologie* 25 (1889): 136–160.
- Duckworth, Dyce. "On a Case of Myxoedema, or Universal Mucinoid Degeneration of the Connective Tissue of the Body." *Transactions of the Clinical Society of London* 8 (1878): 97–98.

- Eiselsberg, Anton Freiherr von. *Die Krankheiten der Schilddrüse*. Stuttgart: Ferdinand Enke, 1901.
- . “Über erfolgreiche Einheilung der Katzenschilddrüse in die Bauchdecke und Auftreten von Tetanie nach deren Exstirpation.” *Wiener Klinische Wochenschrift* 5 (1890): 81–85.
- . “Zur Frage der dauernden Einheilung verpflanzter Schilddrüsen, zugleich ein Beitrag zur postoperativen Tetania.” *Verhandlungen der Deutschen Gesellschaft für Chirurgie* 43 (1890): 655–669.
- Enderlen, Eugen. “Untersuchungen über die Transplantation der Schilddrüse in die Bauchhöhle von Katzen und Hunden.” *Mitteilungen aus den Grenzgebieten der Medizin und Chirurgie* 3 (1898): 474–531.
- Engel, Emil. “Zehn Jahre Beobachteter Fall einer Schilddrüsen Erkrankung.” *Deutsche Medizinische Wochenschrift* 50 (1923): 1378–1379.
- Fagge, C. Hilton. “On Sporadic Cretinism, Occurring in England.” *Medico-chirurgical Transactions* 54 (1871): 155–169.
- Fenwick, E. Harry. “The Diuretic Action of Fresh Thyroid Juice.” *British Medical Journal* 2 (1891): 798.
- Fenwick, Samuel. *The Student’s Guide to Medical Diagnosis*. London: John Churchill, 1869.
- Forster, Michael. *Pathological Physiology*. London: Murray, 1881.
- Gimlette, John D. *Myxoedema and the Thyroid Gland*. London: J.&A. Churchill, 1895.
- Gley, Eugène. “Note préliminaire sur les effets physiologiques du suc de diverses glandes et en particulier du suc extrait de la glande thyroïde.” *Comptes rendus de Société de Biologie* 3 (1891): 250–251.
- . “Sur les fonctions du corps thyroïde.” *Comptes rendus de Société de Biologie* 48 (1891): 429–435.
- Godlee, Rickman J. “Godlee to Clark,” August 28, 1884. ClinSoc 16688.1. Royal Society of Medicine.
- Goodsir, John. “On the Supra-Renal, Thymus and Thyroid Bodies.” *Philosophical Transactions of the Royal Society of London* 136 (1846): 633–641.
- Gowans, William. “History of a Case of Myxoedema.” *British Medical Journal* 1 (1882): 772–773.
- Groves, Ernest W. Hey, and Cecil Joll. “Thyroid and Its Treatment.” *British Medical Journal* no. 2 (1919): 1965–1968.
- . “Thyroid Grafting and Surgical Treatment of Exophthalmic Goitre.” *British Medical Journal* 2 (1910): 1965–1968.

- Gull, William Withey. "On a Cretinoid State Supervening in Adult Life in Women." *Transactions of the Clinical Society of London* 7 (1873): 180–185.
- Hadden, W. B. "The Nervous Symptoms of Myxoedema." *Brain* 5 (1883): 188–196.
- Hadden, W. B., and John Cavafy. "The Symptoms of Myxoedema." *British Medical Journal* 1 (1883): 188–196.
- Hadden, W. B., John Cavafy, Felix Semon, and James F. Goodhart. "Myxoedema: The Question of Mucin." *Lancet* 2 (1884): 1077.
- Halsted, William S. *An Experimental Study of the Thyroid Gland of Dogs, with Especial Consideration of Hypertrophy of This Gland*. Baltimore: Johns Hopkins Press, 1896.
- Halwood, Gregory, and John Sturgess. "Physiological Investigations into Sporadic Cretinism, as Reported by Sir William Gull." *Edinburgh Medical Journal* 20 (1875): 946–957.
- Hammond, W.A. "On Myxoedema, with Special Reference to Its Cerebral and Nervous Symptoms." *St Louis Clinical Record* 7 (1880): 421–425.
- Harington, Charles Robert, and George Barger. "Chemistry of Thyroxine: Constitution and Synthesis of Desido-Thyroxine." *Biochemical Journal* 21 (1927): 169–183.
- Harley, Vaughan. "The Pathogenesis of Pancreatic Diabetes Mellitus." *British Medical Journal* 2 (1892): 452–454.
- Harrower, George. "Human Thyroid Juice Gained for the Treatment of Myxoedema in a Middle Aged Woman." *Journal of Medical Science* 8 (1904): 14–15.
- Harrower, Henry R. *Outlines of Organotherapy*. Glendale, Cal.: Self-published, 1918.
- Heron, J. R. "Case of Myxoedema in a Man." *British Medical Journal* 1 (1882): 89.
- Holland, J. W. "Remarks Upon a Case of Myxoedema." *American Practitioner* 26 (1882): 129–134.
- Hopkins, J. "Case of Myxoedema." *Lancet* 2 (1881): 1021.
- Horsley, Victor Alexander Hayden. "Experimental and Clinical Contributions of Thyroid Tissue Replacement." *International Clinics* 16 (1906): 150–154.
- . "Experimental Transplantation of the Thyroid in Rhesus Macaques, Containing a Histological Analysis." *Transactions of the Pathological Society of London* 41 (1890): 212–215.
- . "Functional Hypertrophy of Grafted Thyroid Tissues." *Transactions of the Pathological Society of London* 42 (1890): 116–122.
- . "Further Researches into the Function of the Thyroid Gland and into the Pathological State Produced by Removal of the Same" (1886): 6–9.
- . MMC/2/MurrayG/1/4. "MS Copies of Letters Sent from Victor Horsley to George Murray." MMC/2/MurrayG/1/4, 1890. John Rylands University Library of Manchester.

- . “Note on a Possible Means of Arresting the Progress of Myxoedema, Cachexia Strumipriva, and Allied Diseases.” *British Medical Journal* 1 (1887): 287–288.
- . “On the Conditions of Thyroid Transplantation.” *Transactions of the Clinical Society of London* 24 (1891): 212–216.
- . “On the Function of the Thyroid Gland.” *Proceedings of the Royal Society of London* 38 (1885): 5–7.
- . “Preventing Cretinism? An Englishman’s Perspective.” *Physiological Review* 3 (1887): 586–626.
- . “Remarks on the Function of the Thyroid Gland: a Critical and Historical Review.” *British Medical Journal* no. 1 (1892): 215–219.
- . “Some Researches Carried Out During the Last Ten Years into the Functions of the Brain and the Thyroid Gland.” London, 1899. Wellcome Manuscript Collection.
- . “The Brown Lectures on Pathology.” *British Medical Journal* 1 (1885): 111–115, 211–213.
- . “Thyroid.” London, 1896. Wellcome Manuscript Collection; MS 6029/2.
- Huskins, Eugene. “On the Question of Thyroid Transplantation.” *The Lancet* 2 (1912): 987–988.
- . “Transplantation of Thyroid Tissue.” *Glasgow Medical Journal* 7 (1891): 28–35.
- Inglis, W. “Two Cases of Myxoedema.” *Lancet* 2 (1880): 864.
- Jabouley, M. “La greffe de corps thyroïde et de capsules surrénales dans les maladies de ces glandes.” *La Médicale Revue Lyonnaise de Médecine* 84 (1897): 399–400.
- Kendall, Edward Calvin “The Isolation of a Compound Containing Iodine in the Thyroid.” *Journal of the American Medical Association* 64 (1915): 2042–2043.
- Kendall, Edward Calvin, and A.E. Osterberg. “The Chemical Identification of Thyroxine.” *The Journal of Biological Chemistry* 40 (1919): 265–334.
- Knauer, Sigfrid. “Organtransplantationen.” In *Die Freien Transplantationen*, edited by Erich Lexer, 1:17–186. Stuttgart: Enke, 1912.
- Kocher, Theodor. “Concerning Pathological Manifestations in Low-grade Thyroid Diseases.” In *Nobel Lectures: Physiology or Medicine, 1901-1921*, 330–383. Amsterdam: Elsevier, 1967.
- . “Die Indicationen zur Kropfexstirpation beim gegenwärtigen Stande der Antisepsis.” *Correspondenzblatt für Schweizer Ärzte* 9 (1892): 225–236, 260–267.
- . “Die Pathologie der Schilddrüse. Zweites Referat.” In *Verhandlungen des Congresses für Innere Medicin*, 9:59–98. Wiesbaden: Bergmann, 1890.

- . “Die Schilddrüsenfunktion im Lichte neuer Behandlungsmethoden verschiedener Kropfformen.” *Correspondenzblatt für Schweizer Ärzte* 25 (1895): 3–21.
- . “Ein Fall von Kachexia mit Struma.” *Correspondenzblatt für Schweizer Ärzte* 21 (1891): 143.
- . “Über die Bedingungen erfolgreicher Schilddrüsenimplantation beim Menschen.” *Verhandlungen der Deutschen Gesellschaft für Chirurgie* 43 (1914): 484–566.
- . “Über Kropfextirpation und ihre Folgen.” *Archiv für Klinische Chirurgie* 29 (1883): 1–84.
- Kreuter, E. “Schilddrüsen und Therapie beim Menschen.” *Zentralblatt für Chirurgie* 46 (1919): 538–540.
- Lancaster, Abraham. “Notes and Reflections on the Thyroid and Its Relation to Disease.” *Lancet* 132 (1888): 1134–1135.
- The Lancet. “Liverpool.” *The Lancet* 1 (1901): 1537.
- . “Brown-Séquard’s ‘Elixir of Life’ (New York, from Our Correspondent).” *The Lancet* 1 (1890): 57–58.
- Lannelongue, Odilon Marc. “Transplantation du Corps Thyroïde.” *Le Bulletin Médicale* 4 (1889): 225.
- Larting, Christopher. “On Thyroid Surgery and Its Practical Importance.” *Archive of Clinical Science* 84 (1907): 208–222.
- Lawson, David. “On the Prognosis of Cretinism.” *Archives of Diseases in Childhood* 30 (1855): 75–82.
- Lediard, J. “Case of Myxoedema.” *Lancet* 1 (1879): 366.
- Leyden, E. von, and Emil Pfeiffer, eds. *Verhandlungen des Kongresses für Innere Medizin, Dreiundzwanzigster Kongress. Gehalten zu München, vom 23.-26. April 1906*. Wiesbaden: Bergmann, 1906.
- Logan, Jerome John. “Surgical Thyroid Disease.” *British Medical Journal* no. 2 (1916): 995–996.
- Lombard, Henry-Claude. “Sur Les Fonctions Du Corps Thyroïde D’après Des Documents Recents.” *Revue Médicale de La Suisse Romande* 3 (1883): 594–6–4.
- Lombroso, Ugo. “Die Gewebselemente, welche die innere Sekretion besorgen.” *Ergebnisse der Physiologie* 9 (1910): 1–89.
- Lubarsch, Otto. “Über Gewebsembolien und Gewebsverlagerungen.” In *Verhandlungen der Deutschen Pathologischen Gesellschaft*, 97–103. Berlin: Fischer, 1899.
- Lydston, Frank G. “Further Therapeutic Possibilities of Organ Replacement.” *New York Medical Journal* 105 (1919): 813–827.

- . "Implantations of the Thyroid Gland and Its Therapeutic Possibilities." *Edinburgh Medical Journal* 100 (1914): 745–753, 812–819, 862–870.
- . "Therapeutic Possibilities of Organ Replacement." *New York Medical Journal* 100 (1914): 745–753, 812–819, 862–870, 913–918.
- Lynn-Thomas, John, and Albert Kocher. "Gleanings from the Story of the Thyroid Gland: An Address Delivered to the South-West Wales Division of the British Medical Association." *British Medical Journal* 1 (1927): 91–94.
- Mackenzie, Hector W.G. "A Case of Myxoedema Treated with Great Benefit by Feeding with Fresh Thyroid Glands." *British Medical Journal* (1892): 940–941.
- . "Die Pathologie der Schilddrüse. Zweites Referat." In *Verhandlungen des Congresses für Innere Medicin*, 9:59–98. Wiesbaden: Bergmann, 1890.
- . "The Treatment of Diabetes Mellitus by Means of Pancreatic Juice." *British Medical Journal* 1 (1893): 63–34.
- Macpherson, John. "Notes on Experimental Thyroid Grafting." *Edinburgh Medical Journal* 35 (1890): 1021–1024.
- Marchand, F. *Der Process der Wundheilung*. Stuttgart: Enke, 1901.
- Mayor, A. "La Cachexie Pachydermique." *Revue Médicale de La Suisse Romande* 3 (1883): 532–539.
- McCarrison, Robert. *The Thyroid Gland in Health and Disease*. New York: William Wood, 1917.
- McClelland, John. "Observations on Goitre." *Transactions of the Medical and Physical Society of Calcutta* 7 (1834): 145–155.
- McLeod, John James R. *Myxoedema: Its Pathological Physiology*. London: Arnold, 1913.
- Mercer, A.C. "Myxoedema." *Medical Record* 19 (1881): 421–425.
- Merklen. "Sur un cas de myxo amélioré par la greffe thyroïdienne." *La Semaine Médicale* 10 (1890): 426.
- Moll, Albert. *Ärztliche Ethik: die Pflichten des Arztes in allen Beziehungen seiner Thätigkeit*. Stuttgart: Enke, 1902.
- Münchener Medizinische Wochenschrift. "Bericht Zur Literatur" 72 (1925): 35–38.
- Murray, George Redmayne. "An Address on the Signs of Early Disease of the Thyroid Gland." *British Medical Journal* 1 (1909).
- . "Bacteriology and the Medical Curriculum." *British Medical Journal* no. 2 (1896): 906.
- . "Discussion on Exophthalmic Goitre." *British Medical Journal* 2 (1922).
- . *Diseases of the Thyroid Gland: Myxoedema and Cretinism*. London: H.K. Lewis, 1900.
- . *Illustrations of the Inductive Method in Medicine*. London: H.K. Lewis, 1891.

- . "Indications for Surgical Treatment of Toxic Goitre." *British Medical Journal* 2 (1927): 774–777.
- . "Note on the Treatment of Myxoedema by Hypodermic Injections of an Extract of the Thyroid Gland of a Sheep." *British Medical Journal* 2 (1891): 796–797.
- . "Notes on the Treatment of Myxoedema." *British Medical Journal* (1891): 796–797.
- . "Remarks on the Treatment of Myxoedema with Thyroid Juice, with Notes of Four Cases." *British Medical Journal* 2 (1892): 449–450.
- . "Some Advances in General and Preventive Medicine Due to Comparative Pathology." *The Lancet* no. 1 (1894): 730–733.
- . "The Clinical History and Symptoms of 120 Cases of Exophthalmic Goitre." *The Lancet* no. 1 (1902): 612–616.
- . "The Life-History of the First Case of Myxoedema Treated by Thyroid Extract." *British Medical Journal* 1 (1920): 334–335.
- . "The Treatment of Exophthalmic Goitre and Other Forms of Hyperthyroidism." *The Lancet* no. 1 (1923): 293–294.
- . "Three Cases of Sporadic Cretinism." *The Lancet* no. 2 (1909): 770–772.
- Natrass, J. H. "Autoplastic Thyroid Transplantation." *British Medical Journal* no. 1 (1923): 1051–1052.
- Norris, Hugh. "Notice of a Remarkable Disease, Analogous to Cretinism, Existing in the West of England." *The Medical Times* 17 (1847): 257–258.
- Oliver, Thomas. "Clinical Lecture on Myxoedema." *British Medical Journal* 1 (1883): 502–504.
- Ord, William Miller. "Clinical Lecture on Myxoedema." *British Medical Journal* (1878): 671–672.
- . "On Myxoedema, a Term Proposed to Be Applied to an Essential Condition in the Cretinoid Affection Occasionally Observed in Middle-aged Women." *Medico-chirurgical Transactions* 61 (1878): 57–78.
- . *On Some Disorders of Nutrition Related with Affections of the Nervous System (Neurotic Dystrophies)*. London: Harrison and Sons, 1884.
- . "On the French 'Method' of Organotherapy." *Transactions of the Clinical Society of London* 23 (1890): 213–214.
- . "Ord to Hadden," April 16, 1887. Wellcome Manuscript Collection.
- . "The Present State of Myxoedema: Being a Discussion of the Relevant Clinical Signs of the Disease." *British Medical Journal* 2 (1890): 1460–1461.
- Ord, William Miller, John Cavafy, Arthur E. Durham, Rickman J. Godlee, James F. Goodhart, W. D. Halliburton, Warrington Haward, et al. *Report of a Committee of the Clinical Society*

of London Nominated December 14, 1883, to Investigate the Subject of Myxædema. Vol. 21 (Supplement). London: Longmans, Green & Co., 1888.

Parker, W. Rushton, John Thomson Telford-Smith, Victor Alexander Hayden Horsley, Fletcher Beach, and G.E Shuttleworth. "A Discussion on Sporadic Cretinism in This Country and Its Treatment." *British Medical Journal* 2 (1896): 620–639.

Pflüger, Eduard. "Abwehr Gegen Meine Kritiker." *Pflüger's Archiv Für Die Gesamnte Physiologie Des Menschen Und Der Thiere* 110 (1903): 1–120.

———. *Das Glykogen und seine Beziehungen zur Zuckerkrankheit*. 2nd ed. Bonn: Hager, 1905.

———. "Die Bedeutung der Neuesten Arbeiten über die Interne Sekretion: Vorläufige Mitteilungen." *Pflüger's Archiv für die gesammte Physiologie des Menschen und der Thiere* 106 (1905): 168–172.

———. "Ein Beitrag zur Frage des im Pankreasdiabetes ausgeschiedenen Zuckers." *Pflüger's Archiv für die gesammte Physiologie des Menschen und der Thiere* 108 (1905): 115–188.

———. "Experimental-Untersuchungen über das Myxödem." *Pflüger's Archiv für die gesammte Physiologie des Menschen und der Thiere* 128 (1909): 125–135.

———. "Ob die Totalexstirpation der Schilddrüse mit Notwendigkeit das Myxoedem Bedingt." *Pflüger's Archiv für die gesammte Physiologie des Menschen und der Thiere* 106 (1905): 181–188.

———. "Parabiose und das Myxödem." *Pflüger's Archiv für die gesammte Physiologie des Menschen und der Thiere* 124 (1908): 633–638.

———. "Über die im Tierischen Körper sich vollziehende Bildung von Zucker aus Eiweiß und Fett: Zur Lehre vom Diabetes Mellitus." *Pflüger's Archiv für die gesammte Physiologie des Menschen und der Thiere* 103 (1904): 1–66.

———. "Über die im tierischen Körper sich vollziehende Bildung von Zucker aus Eiweiß und Fett: Zur Lehre vom Diabetes mellitus." *Pflüger's Archiv* 106 (1904): 1–66.

———. "Über die Natur der Kräfte durch welche die Schilddrüse den Stoffwechsel Beeinflußt." *Pflüger's Archiv für die gesammte Physiologie des Menschen und der Thiere* 119 (1907): 227–248.

Pratt, Joseph H. "The Internal Function of the Thyroid." *Journal of the American Medical Association* 59 (1912): 322–325.

Pybus, Frederick Charles "Notes." *The Lancet* no. 2 (1924): 550–551.

———. "Notes on Thyroid Grafting." *The Lancet* 2 (1924): 550–551.

Ransohoff, Joseph. "On the Normal and Pathological Morphology of the Thyroid." *Annals of Surgery* 19, no. 1 (1894): 78–84.

Reid, James. "On the History and Cause of Bronchocele or Goitre." *The Edinburgh Medical and Surgical Journal* 46 (1836): 40–76.

- Reverdin, J. L., and A. Reverdin. "Note sur vingt-deux operations de goitre." *Revue Médicale de la Suisse Romande* 3 (1883): 169–198, 233–278, 309–364.
- Ridel-Saillard, Georges. *De la Cachexie Pachydermique (myxoedème des auteurs anglais)*. Paris: A. Delahaye & E. Lecrosnier, 1881.
- Robin, V. "Myxoedème traité par le greffe des corps thyroid des moutons." *Gazette Hebdomadaire de Médecine et de Chirurgie* 27 (1890): 451–453.
- Robinson, J. A. "Myxoedema." *Chicago Medical Journal and Examiner* 47 (1883): 467–473.
- Robinson, William. *Endemic Goitre or Thyreocele*. London: Churchill, 1883.
- Schiff, J. Moritz. "Bericht über eine Versuchsreihe betreffend der Wirkungen der Exstirpation der Schilddrüse." *Archiv für Experimentelle Pathologie und Pharmakologie* 18 (1884): 25–34.
- . "Resume d'une nouvelle serie d'expériences sur les effets de l'ablation des corps thyroïde." *Revue Médicale de la Suisse Romande* 4 (1884): 25–34.
- Schöne, Georg. *Eigene Untersuchungen und Vergleichende Studien*. Berlin: Springer, 1912.
- . "Experimentelle Untersuchungen über den therapeutischen Effekt körperfremder Gewebe." *Verhandlungen der Deutschen Gesellschaft für Chirurgie* 37 (1908): 174–178.
- Sharpey-Schäfer, Edward. *History of the Physiological Society During Its First Fifty Years, 1876-1926*. Issued by the Society and Published as a Supplement to the Journal of Physiology. London: Cambridge University Press, 1927.
- Shaw, H. Batty. *Organotherapy or Treatment by Means of Preparations of Various Organs*. Chicago: W.T. Keener, 1905.
- Sick, Paul. "Über die totale Exstirpation einer kropfig entarteten Schilddrüse und über die Rückwirkung dieser Operation auf die Circulationsverhältnisse am Kopfe." *Medizinisches Korrespondenzblatt des Württembergischen ärztlichen Vereins* 37 (1867): 199–205.
- Smith, E. Archibald. "Thyroid Replacement." *British Medical Journal* no. 1 (1911): 166.
- Ssoblew, L. W. "Zur Normalen und Pathologischen Morphologie der Inneren Sekretion." *Virchow's Archiv* 168 (1902): 91–128.
- Stanley, L. L. "An Analysis of One Thousand Thyroidal Substance Implantations." *Endocrinology* 6 (1922): 787–794.
- . "Thyroidal Substance Implantation." *Endocrinology* 5 (1921): 708–714.
- Starling, Ernest H. "Croonian Lecture: On the Chemical Correlation of the Functions of the Body I." *The Lancet* 2 (1905): 339–341.
- . "Croonian Lecture: On the Chemical Correlation of the Functions of the Body II." *The Lancet* 2 (1905): 423–425.

- . “Croonian Lecture: On the Chemical Correlation of the Functions of the Body III.” *The Lancet* 2 (1905): 501–503.
- . “Croonian Lecture: On the Chemical Correlation of the Functions of the Body IV.” *The Lancet* 2 (1905): 579–583.
- Stich, Rudolf. “Über den heutigen Stand der Organtherapie.” *Deutsche Medizinische Wochenschrift* 39 (1913): 1865–1868.
- Storer, Malcolm. “On Thyroid Replacement.” *Boston Medical and Surgical Journal* 172 (1915): 41–46.
- Tiberti, Nuno, and Andrea Franchetti. “Sur les effets de l’extirpation partielle et de l’extirpation totale du thyroïde chez le chiens.” *Archives italiennes de Biologie* 51 (1909): 127–131.
- Turrington, Charles. “The Extirpation of the Thyroid Gland: An Experimental Study.” *Archive for Experimental Pathology* 21 (1886): 387–460.
- Variot, G. “Trois experiences sur l’action physiologique du suc testiculaire injecté sous la peau, suivant la method de M. Brown-Séquard.” *Comptes rendus de Société de Biologie* 1 (1889): 451–454.
- Verhandlungen der Deutschen Gesellschaft für Chirurgie. “37th Congress,” 1908.
- Virchow, Rudolf. “Krankheitswesen und Krankheitsursachen.” *Virchow’s Archiv* 79 (1880): 1–19, 185–228.
- Wells, Herbert George. *The Island of Doctor Moreau*. London: Stone and Kimball, 1896.
- White, W. Hale. “On the Treatment of Diabetes Mellitus by Feeding on Raw Pancreas and the Subcutaneous Injection of Liquor Pancreaticus.” *British Medical Journal* 1 (1893): 452–453.
- Williams, Leonard. “Adenoids, Nocturnal Incontinence, and the Thyroid Gland.” *The Lancet* 173 (1909): 1245–1247.
- Williams, P. Watson. “Notes on Myxoedema Treated with Extract and Graft of Sheep’s Thyroid.” *British Medical Journal* 2 (1894): 1303–1304.
- . “Transplantation of Thyroid in Myxoedema.” *British Medical Journal* 1 (1903): 580.
- Wood, Kinder. “Observations Upon the Local Prevalence of Idiotism, and Its Connection with Goitre.” *The Edinburgh Journal of Medical Science* 2 (1826): 194–198.
- Wood, Neville. “The Treatment of Diabetes by Pancreatic Extracts.” *British Medical Journal* 1 (1893): 64.
- Wu, P. P. T., and Frank C. Mann. “Histologic Studies.” *Archives of Surgery* 28 (1934): 889–908.

SECONDARY SOURCES

- Ackerknecht, Erwin H. *Medicine in the Paris Hospital 1794-1848*. Baltimore: Johns Hopkins University Press, 1966.
- Ahmed, A.M., and N.H. Ahmed. "History of Disorders of Thyroid Dysfunction." *Eastern Mediterranean Health Journal* 11 (2005): 459–469.
- Aminoff, Michael J. *Brown-Séquard: An Impossible Genius Who Transformed Medicine*. Oxford: Oxford University Press, 2011.
- Arrizabalaga, Jon. "Problematizing Retrospective Diagnosis in the History of Disease." *Asclepio* 54 (2002): 51–70.
- Banks, Emily. "From Dogs' Testicles to Mares' Urine: The Origins and Contemporary Use of Hormonal Therapy for the Menopause." *Feminist Review* (2002): 2–25.
- Ben-David, Joseph. *The Scientist's Role in Society: a Comparative Study*. Englewood Cliffs, N.J.: Prentice-Hall, 1971.
- Bishop, P.M.F. "The Development of British Endocrinology." *British Medical Journal* (1955): 866–870.
- Bleker, Johanna. *Die Naturhistorische Schule*. Medizin in Geschichte und Kultur. Stuttgart: Fischer, 1981.
- Bliss, Michael. *The Discovery of Insulin*. Toronto: University of Toronto Press, 2007.
- Bonner, Thomas Neville. *Becoming a Physician: Medical Education in Britain, France, Germany, and the United States, 1750-1945*. Baltimore: Johns Hopkins University Press, 2000.
- Borell, Merriley Elaine. "Brown-Sequard's Organotherapy and Its Appearance in America at the End of the Nineteenth Century." *Bulletin of the History of Medicine* 50 (1976): 309–320.
- . "Organotherapy, British Physiology, and Discovery of the Internal Secretions." *Journal of the History of Biology* 9 (1976): 235–268.
- . "Origins of the Hormone Concept." PhD Thesis, Yale University, 1976.
- . "Setting the Standards for a New Science: Edward Schäfer and Endocrinology." *Medical History* 22, no. 3 (1978): 282–290.
- Bornhauser, Sigmund. *Zur Geschichte der Schilddrüsen- und Kropfforschung im 19. Jahrhundert unter besonderer Berücksichtigung der Schweiz*. Aarau: H.R. Sauerländer, 1951.
- Bos, Michael A. *Organ Replacement Therapy: New Advances in an Ancient Method*. London: King's Fund Centre, 1991.
- Boschung, Urs, ed. *Theodor Kocher 1841-1917*. Bern: Hans Huber, 1991.

- Bradley, Graham W. *Disease, Diagnosis and Decisions*. Chichester: Wiley & Sons, 1993.
- Broadbent, Alex. "Causation and Models of Disease in Epidemiology." *Studies in History and Philosophy of Biological and Biomedical Sciences* 40 (2009): 302–311.
- Brügelmann, Jan. *Der Blick Des Arztes Auf Die Krankheit Im Alltag 1779-1850*. Berlin: Freie Universität Berlin, 1982.
- Bynum, William F. "'C'est Un Malade': Animal Models and Concepts of Human Disease." *Journal of the History of Medicine and Allied Sciences* 45 (1990): 397–413.
- . *Science and the Practice of Medicine in the Nineteenth Century*. Cambridge: Cambridge University Press, 1994.
- Cameron, Hector Charles. *Mr Guy's Hospital, 1726-1948*. London: Longmans, Green & Co., 1954.
- Canguilhem, Georges. *The Normal and the Pathological*. New York: Zone Books, 1989.
- Cardwell, Donald Stephen Lowell. *The Organisation of Science in England*. London: Heinemann, 1972.
- Carter, Kay Codell. "Ignaz Semmelweis, Carl Mayrhofer, and the Rise of Germ Theory." *Medical History* 29 (1985): 33–53.
- . "The Development of Pasteur's Concept of Disease Causation and the Emergence of Specific Causes in Nineteenth-Century Medicine." *Bulletin of the History of Medicine* 65 (1991): 528–548.
- . *The Rise of Causal Concepts of Disease: Case Histories*. History of Medicine in Context. Aldershot: Ashgate, 2003.
- Cawadias, A. P. "The History of Endocrinology." *Proceedings of the Royal Society of Medicine* 34 (1940): 25–30.
- Clarke, Edwin. "Victor Alexander Haden Hayden Horsley." In *Dictionary of Scientific Biography*, edited by C. C. Gillispie, VI:518–519. New York: Charles Scribner's Sons, 1972.
- Clarke, Edwin, and L. S. Jacyna. *Nineteenth-Century Origins of Neuroscientific Concepts*. London: University of California Press, 1987.
- Coleman, William. "The Cognitive Basis of the Discipline: Claude Bernard on Physiology." *Isis* 76 (1985): 49–70.
- Cunningham, Andrew. "Identifying Disease in the Past: Cutting the Gordian Knot." *Asclepio* 56 (2002): 13–34.
- Cunningham, Andrew, and Perry Williams. *The Laboratory Revolution in Medicine*. Cambridge: Cambridge University Press, 1992.
- Dadan, J., and A. Nowacka. "A Journey into the Past: The History of Thyroid Surgery." *Wiadomości Lekarski* 61 (2008): 88–92.

- Delhoume, Léon. *De Claude Bernard a d'Arsonval*. Paris: J.-B. Bailliére, 1939.
- Ekbom, Karl. "The Man Behind the Syndrome: Jean-Martin Charcot." *Journal of the History of the Neurosciences* 1 (1992): 39–45.
- Elkeles, Barbara. "Die Schweigsame Welt von Arzt und Patient: Einwilligung und Aufklärung in der Arzt-Patienten-Beziehung des 19. und frühen 20. Jahrhunderts." *Medizin, Gesellschaft und Geschichte* 8 (1989): 63–91.
- Encyclopaedia Britannica. "Charles Edward Brown-Séguard." In *Encyclopaedia Britannica*, IV:674. 11th ed., 1910.
- Eulner, Hans-Heinz. *Die Entwicklung der Medizinischen Spezialfächer an den Universitäten des Deutschen Sprachgebietes*. Stuttgart: Ferdinand Enke, 1970.
- Faden, Ruth R, and Tom L Beauchamp. *A History and Theory of Informed Consent*. New York: Oxford University Press, 1986.
- Fagot-Largeault, Anne M. "On Medicine's Scientificity: Did Medicine's Accession to Scientific 'Positivity' in the Course of the Nineteenth Century Require Giving up Causal (Etiological) Explanation?" In *Science, Technology, and the Art of Medicine: European-American Dialogues*, edited by Corinna Delkeskamp-Hayes and Mary Ann Gardell Cutter, 105–126. Dordrecht: Kluwer, 1993.
- Fantini, Bernardino. "La révolution pastoriennne et les théories sur l'étiologie du goitre et du crétinisme." *Gesnerus* 49 (1992): 21–38.
- Feinstein, Alvan R. *Clinical Judgement*. Baltimore: Williams & Wilkins, 1967.
- Fischer, Isidore. *Biographisches Lexikon der hervorragenden Ärzte der letzten Fünfzig Jahre*. 2 vols. Reprint. Munich: Urban & Schwarzenberg, 1962.
- Foucault, Michel. *The Birth of the Clinic: An Archaeology of Medical Perception*. Routledge, 2003.
- Fox, Renée C, and Judith P Swazey. *Spare Parts: Organ Replacement in American Society*. New York: Oxford University Press, 1992.
- . *The Courage to Fail: A Social View of Organ Replacement and Dialysis*. Chicago: Chicago University Press, 1974.
- French, Richard D. *Antivivisection and Medical Science in Victorian Society*. Princeton, N.J.: Princeton University Press, 1975.
- Galdstone, Iago. "The Romantic Period in Medicine." *Bulletin of the New York Academy of Medicine* 35, no. 5 (1956): 346–362.
- Ginn, Sheryl R., and Joel A. Vilensky. "Experimental Confirmation by Sir Victor Horsley of the Relationship Between Thyroid Gland Dysfunction and Myxedema." *Thyroid* 16 (2006): 743–747.
- Gittes, Ruben F. "Endocrine Tissues." In *Transplantation*, edited by John S. Najarian and Robert L. Simmons, 698–710. Munich: Schwarzenberg, 1972.

- Gradmann, Christoph. *Krankheit im Labor: Robert Koch und die medizinische Bakteriologie*. Göttingen: Wallstein, 2005.
- Grinnell, George C. "The Physiology of Romantic Medicine." *Studies in Romanticism* 45, no. 2 (2006): 223–250.
- Hamilton, David. *A History of Organ Transplantation: Ancient Legends to Modern Medicine*. Pittsburgh: University of Pittsburgh Press, 2012.
- . *The Monkey Gland Affair*. London: Chatto & Windus, 1986.
- Harrison, Donald. *Felix Semon 1849-1921: A Victorian Laryngologist*. Eponymists in Medicine. London: Royal Society of Medicine Press, 2000.
- Healy, Kieran J. *Last Best Gift: Altruism and the Market for Human Blood and Organs*. Chicago: University of Chicago Press, 2006.
- Hendriksen, Jens H. *Starling, His Contemporaries and the Nobel Prize: One Hundred Years with Hormones*. Oslo: Taylor and Francis, 2003.
- Hess, Volker. *Von der Semiotischen zur Diagnostischen Medizin*. Vol. 66. Abhandlungen zur Geschichte der Medizin und der Naturwissenschaften. Husum: Matthiesen Verlag, 1993.
- Hoffman, Frederick G. "The Fifth Anniversary." *Endocrinology* 80 (1967): 1–4.
- Holtdorf, Kent. *Hormone Replacement Therapy and the Biodental Debate: Are They Really Safer and More Effective Than Synthetic Hormones?* Today Radio, 2010.
- Hughes, A F, and Margaret Wells Egar. "A History of Endocrinology." *Journal of the History of Medicine and Allied Sciences* 32 (1977): 292–313.
- Isepponi, Oliver, Valentin Huwiler, and Urs Boschung. "Theodor Kocher's Surgical and Clinical Case Presentations." *Bulletin of the History of Medicine* 78 (2004): 192–194.
- Jewson, Nicholas D. "Medical Knowledge and the Patronage System in Eighteenth Century England." *Sociology* 8 (1974): 369–385.
- . "The Disappearance of the Sick Man from Medical Cosmology." *Sociology* 10 (1976): 225–244.
- Jordanova, Ludmilla. *Sexual Visions: Images of Gender in Science and Medicine Between the Eighteenth and Twentieth Centuries*. Madison: University of Wisconsin Press, 1989.
- . "The Social Construction of Medical Knowledge." *Social History of Medicine* 8 (1995): 361–381.
- Kanner, Leo. "Johann Jakob Guggenbühl and the Abendberg." *Bulletin of the History of Medicine* 33 (1959): 489–502.
- King, Lester S. *Medical Thinking: A Historical Preface*. Princeton, N.J.: Princeton University Press, 1982.

- Lachmund, Jens, and Gunnar Stollberg, eds. *The Social Construction of Illness: Illness and Medical Knowledge in Past and Present*. Stuttgart: Steiner, 1992.
- Lacquer, Thomas Walter. *Solitary Sex: A Cultural History of Masturbation*. New York: Zone Books, 2003.
- Langdon-Brown, Walter. "The Birth of Modern Endocrinology." *Proceedings of the Royal Society of Medicine* 39 (1946).
- . *The Integration of the Endocrine System*. Cambridge: Cambridge University Press, 1935.
- Langer, Peter. "History of Goitre." *World Health Organization Monograph Series* 44 (1960): 9–26.
- Latour, Bruno. *Science in Action*. Cambridge, Mass.: Harvard University Press, 1987.
- . *The Pasteurization of France*. Cambridge, Mass.: Harvard University Press, 1988.
- Latour, Bruno, and Steve Woolgar. *The Social Construction of Scientific Facts*. Beverly Hills: Sage Publications, 1979.
- Lawrence, Christopher. "A Tale of Two Sciences: Bedside and Bench in Twentieth Century Britain." *Medical History* 43 (1999): 421–449.
- . "Democratic, Divine, and Heroic: The History and Historiography of Surgery." In *Medical Theory and Surgical Practice: Studies in the History of Surgery*. The Wellcome Institute Series in the History of Medicine. London: Routledge, 1992.
- . "Incommunicable Knowledge: Science, Technology and the Clinical Art in Britain, 1850-1914." *Journal of Contemporary History* 20 (1985): 503–520.
- . *Medicine in the Making of Modern Britain, 1700-1920*. London: Routledge, 1994.
- . *Rockefeller Money, the Laboratory and Medicine in Edinburgh 1919-1930: New Science in an Old Country*. Rochester Studies in Medical History. Rochester, NY: University of Rochester Press, 2005.
- Lederer, Susan E. *Flesh and Blood: Organ Transplantation and Blood Transfusion*. New York: Oxford University Press, 2008.
- . *Subjected to Science: Human Experimentation in America before the Second World War*. Baltimore: Johns Hopkins University Press, 1995.
- Lee, T. "A Brief History of the Endocrine Disorders in China." *Chinese Medical Journal* 59 (1941): 379–386.
- Leoutsakos, Vasilli. "A Short History of the Thyroid Gland." *Hormones* 3 (2004): 268–271.
- Lesch, John E. *Science and Medicine in France: The Emergence of Experimental Physiology, 1790-1855*. Cambridge, Mass.: Harvard University Press, 1984.

- Lindholm, J., and P. Laurberg. "Hypothyroidism and Thyroid Substitution: Historical Aspects." *Journal of Thyroid Research* 2011 (2011): 1–10.
- Lisser, Hans. "The Endocrine Society: The First Forty Years (1917-1957)." *Endocrinology* 80 (1967): 5–28.
- Logan, S.T., and J.S. Logan. "The Treatment of Myxoedema with Raw Sheep Thyroid Gland and Its Introduction into Practice in County Londonderry in 1892." *The Ulster Medical Journal* 61 (1992): 86–93.
- Long Hall, Diana. "Biology, Sex Hormones and Sexism in the 1920's." *Philosophical Quarterly* 5 (1973): 81–96.
- Long Hall, Diana, and Thomas F Glick. "Endocrinology: a Brief Introduction." *Journal of the History of Biology* 9 (1976): 229–233.
- Löwy, Ilana. "Medicine and Change." In *Medicine and Change: Historical and Sociological Studies of Medical Innovation*, edited by Ilana Löwy, 1–20. Paris: John Libbey, 1993.
- . *Medicine and Change: Historical and Sociological Studies of Medical Innovation*. Paris: John Libbey, 1993.
- Lyons, John Benignus. "Sir Victor Horsley." *Medical History* 11 (1967): 361–373.
- Maehle, Andreas-Holger. *Doctors, Honour and the Law: Medical Ethics in Imperial Germany*. Basingstoke: Palgrave Macmillan, 2009.
- Maulitz, Russell C. *Morbid Appearances*. Cambridge: Cambridge University Press, 1987.
- Mauri, Heinrich. *Die Entwicklung des Kretinenproblems: Die Kretinismusforschung im 19. Jahrhundert*. Freiburg: University of Freiburg, 1976.
- McCracken-Flesher, Carolyn. *The Doctor Dissected: a Cultural Autopsy of the Burke & Hare Murders*. Oxford: Oxford University Press, 2012.
- Medvei, Victor Cornelius. *The History of Clinical Endocrinology: A Comprehensive Account of Endocrinology from Earliest Times to the Present Day*. Carnforth: Parthenon, 1993.
- Merke, Franz. *History and Iconography of Endemic Goitre and Cretinism*. Lancaster: MTP Press, 1984.
- Montgomery, Kathryn. *How Doctors Think: Clinical Judgment and the Practice of Medicine*. Oxford: Oxford University Press, 2006.
- Moore, Francis D. *Give and Take: The Development of Tissue Transplantation*. Philadelphia: Saunders, 1964.
- Morgan, Neil. "William Dobinson Halliburton, F.R.S. (1860-1931): Pioneer of British Biochemistry?" *Notes and Records of the Royal Society of London* 38 (1983): 129–145.
- Nutton, Vivian. *Ancient Medicine*. Series of Antiquity. London: Routledge, 2004.

- Olmsted, J.M.D. *Charles-Éduard Brown-Séquard: A Nineteenth Century Neurologist and Endocrinologist*. Baltimore: Johns Hopkins Press, 1946.
- Oudshoorn, Nelly. *Beyond the Natural Body: an Archeology of Sex Hormones*. London: Routledge, 1994.
- Paget, Stephen. *Sir Victor Horsley*. New York, 1920.
- Parker, James N., and Philip M. Parker. *Myxoedema: A Medical Dictionary, Bibliography, and Annotated Research Guide to Internet References*. San Diego, CA: Icon, 2004.
- Peset, José, and Gracia Diego. *The Ethics of Diagnosis*. Vol. 40. Kluwer, 1992.
- Pickstone, John V. "Introduction." In *Medical Innovations in Historical Perspective*, edited by John V Pickstone, 1–16. Basingstoke: Macmillan, 1992.
- . "Objects and Objectives: Notes on the Material Cultures of Medicine." In *Technologies of Modern Medicine*, edited by Ghishlane Lawrence, 13–24. London: Science Museum, 1994.
- . "The Biographical and the Analytical: Towards a Historical Model of Science and Practice in Modern Medicine." In *Medicine and Change: Historical and Sociological Studies of Medical Innovation*, edited by Ilana Löwy, 23–42. Paris: John Libbey, 1993.
- . *Ways of Knowing: a History of Science, Technology and Medicine*. Manchester: Manchester University Press, 2000.
- . "Ways of Knowing: Towards a Historical Sociology of Science, Technology and Medicine." *British Journal for the History of Science* 26 (1993): 433–458.
- Power, d'Arcy. "Robert Brudenell Carter." In *Plarr's Lives of the Fellows of the Royal College of Surgeons of England*, 1:201–203. London: Royal College of Surgeons, 1930.
- Prüll, Cay-Rüdiger. "Pathology and Surgery in London and Berlin 1800-1930: Pathological Theory and Clinical Practice." In *Pathology in the 19th and 20th Centuries: The Relationship Between Theory and Practice*, 71–91. Sheffield: EAHMH Publications, 1998.
- Prüll, Cay-Rüdiger, and Marianne Sinn. "Problems of Consent to Surgical Procedures and Autopsies in to Twentieth Century Germany." In *Historical and Philosophical Perspectives on Biomedical Ethics: From Paternalism to Autonomy?*, edited by Andreas-Holger Maehle and Johanna Geyer-Kordesch, 73–94. Aldershot: Ashgate, 2002.
- Rolleston, Humphry Davy. "Endocrines in Theory and Practice: The History of Endocrinology." *British Medical Journal* 1 (1937): 1033–1036.
- . "Setting the Standards for a New Science: Edward Schäfer and Endocrinology." *Medical History* 22, no. 3 (1978): 282–290.
- The Endocrine Organs in Health and Disease with an Historical Review*. Oxford: Oxford University Press, 1936.

- Romano, Terrie M. *Making Medicine Scientific: John Burdon Sanderson and the Culture of Victorian Science*. Baltimore: Johns Hopkins University Press, 2002.
- Rosemann, R. "Pflüger's Lebenswerk." *Pflüger's Archiv für die gesamte Physiologie des Menschen und der Thiere* 222 (1929): 548–562.
- Rosenberg, Charles E. "Disease in History: Frames and Framers." *The Milbank Quarterly* 67 (1989): 1–15.
- Rosenberg, Charles E., Janet Golden, Judith Walzer Leavitt, and Morris Vogel, eds. *Framing Disease: Studies in Cultural History*. New Brunswick: Rutgers University Press, 1992.
- Rupke, Nicolaas A. "Pro-vivisection in England in the Early 1880s: Arguments and Motives." In *Vivisection in Historical Perspective*, edited by Nicolaas A. Rupke, 188–213. London: Croom Helm, 1987.
- , ed. *Vivisection in Historical Perspective*. London: Croom Helm, 1987.
- Satzinger, Helga. *Differenz und Vererbung: Geschlechterordnungen in der Genetik und Hormonforschung 1890-1950*. Köln: Böhlau, 2008.
- Sawin, Clark T. "Defining Myxoedema and Its Cause." In *Report of a Committee Nominated December 14, 1883 to Investigate the Subject of Myxoedema; Being a Supplement to Volume 21 of Its Transactions; Facsimile Edition*, 1–14. Boston: The Francis A. Countway Library of Medicine, 1991.
- . "Goitre." In *The Cambridge World History of Human Disease*, 750–756. Cambridge: Cambridge University Press, 1993.
- . "The Invention of Thyroid Therapy in the Late Nineteenth Century." *The Endocrinologist* 11 (2001): 1–3.
- . "Thyroid Hormone Therapy: Origins and Early History." *Thyroid Today* 13, no. 1 (1990): 1–11.
- Schiller, J. "Physiology's Struggle for Independence in the First Half of the Nineteenth Century." *History of Science* 7 (1968): 260–270.
- Schlich, Thomas. "Changing Disease Identities: Cretinism, Politics and Surgery (1844-1882)." *Medical History* 38 (1994): 421–443.
- . *Die Erfindung der Organtransplantation: Erfolg und Scheitern des Chirurgischen Organersatzes*. Frankfurt: Campus, 1998.
- . "Making Mistakes in Science: Eduard Pflüger, His Scientific and Professional Concept of Physiology, and His Unsuccessful Theory of Diabetes." *Studies in History and Philosophy of Science* 23 (1993): 411–441.
- . "Pathological Theory - Surgical Practice? The Rationale Behind the First Organ Transplantation." In *Pathology in the 19th and 20th Centuries: The Relationship Between Theory and Practice*, edited by Cay-Rüdiger Prüll, 55–69. Sheffield: EAHMH Publications, 1998.

- . *The Origins of Organ Transplantation: Surgery and Laboratory Science, 1880-1930*. Rochester, NY: Rochester University Press, 2010.
- Schlich, Thomas, and Ulrich Tröhler. *The Risks of Medical Innovation: Risk Perception and Assessment in Historical Context*. London & New York: Routledge, 2006.
- Sengoopta, Chandak. *The Most Secret Quintessence of Life: Sex, Glands, and Hormones, 1850-1950*. Chicago: University of Chicago Press, 2006.
- Sharp, Lesley. *Strange Harvest: Denatured Bodies and the Transformed Self*. Berkeley, Los Angeles: University of California Press, 2006.
- Siegel-Watkins, Elizabeth. *The Estrogen Elixir : a History of Hormone Replacement Therapy in America*. Baltimore: Johns Hopkins University Press, 2007.
- Silverstein, Arthur M. *A History of Immunology*. San Diego: Academic Press, 1989.
- Simmer, Hans H. "Pflüger's Nerve Reflex Theory: The Product of Analogy, Teleology and Neurophysiology." *Clio Medica* 12 (1977): 57–90.
- Slater, Stefan. "The Discovery of Thyroid Replacement Therapy. Part 1: In the Beginning." *Journal of the Royal Society of Medicine* 104 (2011): 15–18.
- Sturdy, Steve. "Knowing Cases: Biomedicine in Edinburgh, 1887-1920." *Social Studies of Science* 37 (2007): 659–689.
- . "Looking for Trouble: Medical Science and Clinical Practice in the Historiography of Modern Medicine." *Social History of Medicine* 24 (2011): 739–757.
- . "Scientific Method for Medical Practitioners: The Case Method of Teaching Pathology in Early Twentieth-Century Edinburgh." *Bulletin of the History of Medicine* 81 (2007): 760–792.
- Tattersall, Robert. "Pancreatic Organotherapy for Diabetes, 1889-1921." *Medical History* 39 (1995): 288–316.
- . "Quest for Normoglycaemia: a Historical Perspective." *Diabetic Medicine* 11 (1994): 618–635.
- Temkin, Owsei. "The Role of Surgery in the Rise of Modern Medical Thought." *Bulletin of the History of Medicine* 25 (1951): 248–259.
- . "The Scientific Approach to Disease: Specific Entity and Individual Sickness." In *Concepts of Health and Disease: Interdisciplinary Perspectives*, edited by H Tristram Engelhardt, T. H Caplan, and J. J MacCartney, 247–263. Reading, Mass.: Addison-Wesley, 1981.
- The Cambridge World History of Human Disease*. Cambridge: Cambridge University Press, 1993.
- The Lancet. "Before Our Time." *The Lancet* 1 (1965): 315.

- Tomes, Nancy, and John Harley Warner. "Introduction to Special Issue on Rethinking the Reception of the Germ Theory of Disease: Comparative Perspectives." *Journal of the History of Medicine and Allied Sciences* 52 (1997): 7–16.
- Tröhler, Ulrich. "Chirurgie und Ethik." *Gesnerus* 49 (1992): 119–135.
- . *Der Nobelpreisträger Theodor Kocher 1841-1917: Auf dem Weg zur Physiologischen Chirurgie*. Basel: Birkhäuser, 1984.
- . "Die Wechselwirkung von Anatomie, Physiologie und Chirurgie im Werk Theodor Kochers und einiger Zeitgenossen." In *Theodor Kocher 1841-1917*, edited by Urs Boschung, 53–71. Bern: Hans Huber, 1991.
- . "Surgery (Modern)." In *Companion Encyclopaedia of the History of Medicine*, edited by William F Bynum and Roy Porter. Vol. 2. London: Routledge, 1993.
- . "Surgery (Modern)." In *Companion Encyclopaedia of the History of Medicine*, 2:984–1028. London: Routledge, 1993.
- . "'To Operate or Not to Operate?' Scientific and Extraneous Factors in Therapeutical Controversies Within the Swiss Society of Surgery 1913-1988." In *Essays in the History of Therapeutics*, edited by William F Bynum and Vivian Nutton, 89–113. Amsterdam: Rodopi, 1991.
- . "Was ist Therapeutische Erfahrung? Die historische Entwicklung der Therapiebewertung zwischen subjektiv sicherem Wissen und objektiv wahrscheinlichen Kenntnissen." *Deutsches Ärzteblatt* 88 (1991): B–2156–B–2162.
- Tuchman, Arleen Marcia. *Science, Medicine, and the State in Germany: The Case of Baden, 1815-1871*. Oxford: Oxford University Press, 1993.
- Warner, John Harley. "The History of Science and the Sciences of Medicine." *Osiris* 10 (1995): 164–193.
- Welbourne, Richard Burkewood. *The History of Endocrine Surgery*. New York: Praeger, 1990.
- Wilson, G. "The Brown Animal Sanatory Insitution." *Journal of Hygiene* 82 (1979): 155–176, 337–352, 501–521.
- Wilson, Leonard G. "Internal Secretions in Disease: The Historical Relations of Clinical Medicine and Scientific Physiology." *Journal of the History of Medicine and Allied Sciences* 39 (1984): 263–302.
- Woodruff, Michael F. A. *The Transplantation of Tissues and Organs*. Springfield, IL: Thomas, 1960.
- Woolgar, Steve. *Science: The Very Idea*. London: Tavistock, 1988.
- Wright, Peter, and Andrew Treacher, eds. *The Problem of Medical Knowledge: Examining the Social Construction of Medicine*. Edinburgh: Edinburgh University Press, 1982.

Young, F. G. "The Evolution of Ideas About Animal Hormones." In *The Chemistry of Life: Eight Lectures on the History of Biochemistry*, edited by Joseph Needham, 125–155. Cambridge: Cambridge University Press, 1971.

Zloczower, A. "Career Opportunities and the Growth of Scientific Discovery in 19th Century Germany with Special Reference to Physiology." The Hebrew University of Jerusalem, 1966.

APPENDIX: TIMELINE

